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ANNALS OF
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VOLUME 27 DECEMBER 1947 NUMBER 6

# OSTEOPOROSIS *

By FULLER ALBRIGHT, M.D., *Boston, Massachusetts*

DR. WARING, MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS, AND GUESTS!

OSLER is quoted as saying: "If you know syphilis, you know internal medicine." Time and medicine have marched on. I think if Osler were here today he would agree to amend his statement to read: "If you know the adrenal cortex, you know internal medicine." With this in mind, I first chose, as the subject of this lecture, "Adrenal Cortical Syndromes and Their Diagnoses." But I soon found I did not know the adrenal cortex!

I think I do understand a few things about osteoporosis, which, like everything else, is intimately connected with the adrenal cortex.

## NORMAL INTERNAL DYNAMICS OF THE SKELETON

Before defining osteoporosis, I will give you my working scheme for the normal internal dynamics of the skeleton. I will start by synthesizing a normal middle-aged individual; in so doing I will put in only those structures which concern the present discussion.

First, I will give him an outside skin, and, to add a little realism, four rudimentary appendages (figure 1A); then I will put in a gastrointestinal tract and a kidney with an outlet to the outer world; after that I will fill the body with fluid and set aside one compartment of fluid to represent the blood

* The John Phillips Memorial Lecture read before the American College of Physicians in Chicago on April 30, 1947. For further studies by the author and his colleagues on the subject of osteoporosis the reader is referred to the following references in the bibliography.[1, 2, 3, 4, 5, 6, 7]

From the Medical Service of the Massachusetts General Hospital and the Department of Medicine of the Harvard Medical School, Boston, Massachusetts.

The expense of these studies was partly defrayed by grants from the Josiah Macy, Jr. Foundation, the Rockefeller Foundation, the National Advisory Cancer Council, Ayerst, McKenna and Harrison, Ltd., and the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council. A bed supported by the Mallinckrodt Chemical Company on the Metabolic Ward was used for part of these studies.

The part of this address which has to do with internal skeletal dynamics and osteoporosis of old age was read at the Ether Centenary at the Massachusetts General Hospital on October 14, 1946.

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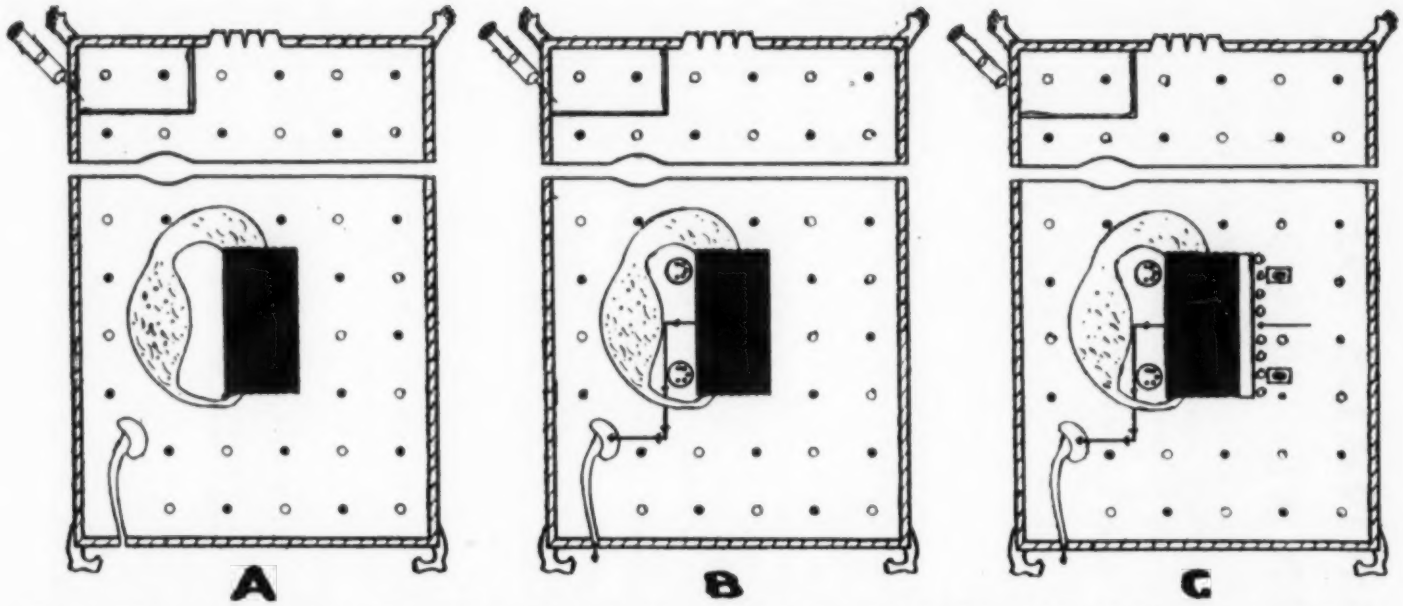


FIG. 1. Diagrammatic synthesis of structures and relationships important for understanding of internal dynamics of skeleton.

(A) Body covering with four rudimentary appendages, four outpocketings to represent teeth, gastrointestinal tract, kidney with outlet to outside, body fluids containing calcium ions (black circles) and phosphate ions (white circles), compartment of body fluids representing serum with a syringe for sampling, a large rectangular black mass representing calcified skeleton, and structure representing muscles attached to skeleton.

(B) Same as (A) plus osteoclasts to represent bone-resorbing surfaces and black arrows to indicate calcium going from bone to kidneys to outside world.

(C) Same as (B) plus osteoblasts on bone-forming surfaces laying down uncalcified matrix, plus localized concentration of phosphate ions on these surfaces and black arrow indicating deposition of calcium therein.

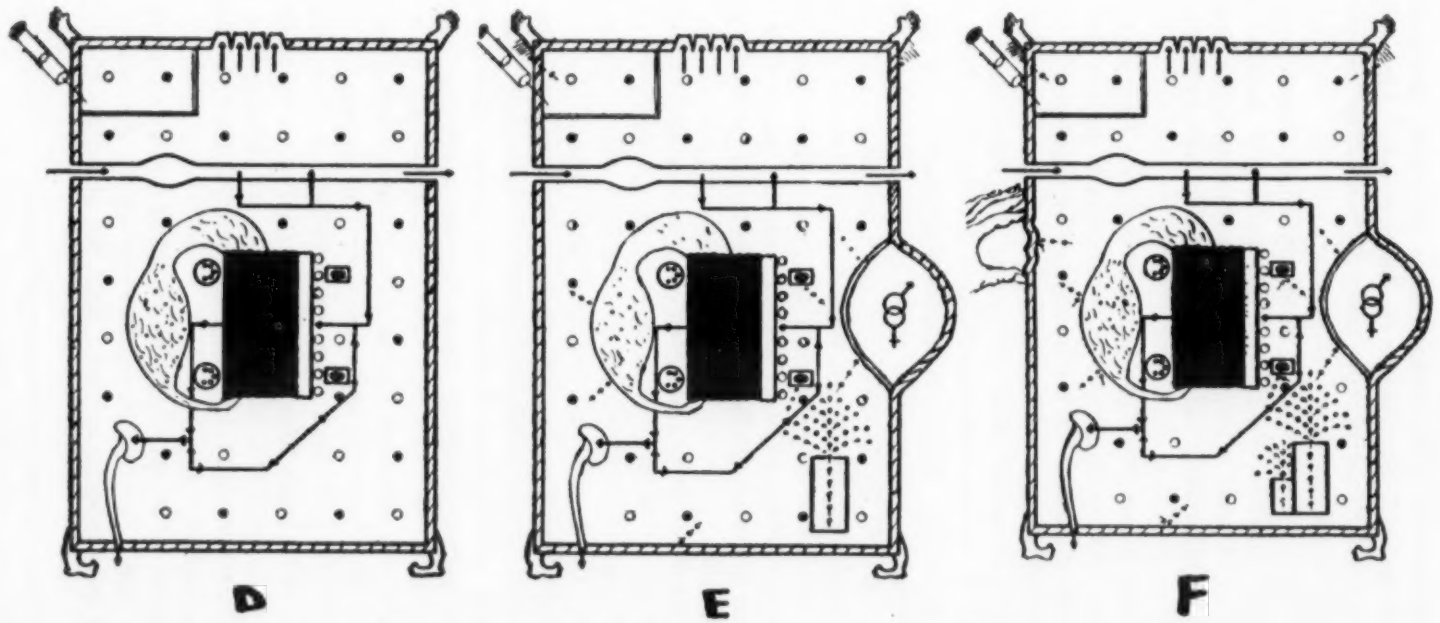


FIG. 1. (D) Same as (C) plus black arrows to indicate movement of calcium in the body.
(E) Same as (D) plus steroid-producing organ in right lower quadrant sending out hormones which stimulate axillary hair growth, secondary sex development, osteoblasts, muscle growth, and skin growth.
(F) Same as (E) plus special wing of steroid organ producing steroids which inhibit osteoblastic activity, muscle growth, and skin growth (see text).

serum. This component is of importance since it can be sampled with a syringe and thus its chemical constituents can be analyzed. Throughout the body fluids I will put calcium ions represented by black dots and phosphate ions represented by white dots.

I will now introduce into the center of this synthetic man a large black quadrangular area to represent the skeleton (figure 1A). At the two ends of this skeleton I will attach a structure which represents the body musculature. Then, I will introduce outpocketings of the body surface to represent the teeth.

The synthesis now becomes a little bit more complex and, I might add, controversial. The skeleton is composed of an organic matrix into which is deposited a calcium-phosphate-carbonate salt, called dahlite. Much of the skeleton is in the form of a maze of interlacing trabeculae so that the surface area is tremendous. From the point of view of internal skeletal dynamics there are two types of surface—one where bone is being laid down and one where it is being resorbed. Where bone is being resorbed one sees osteoclasts which are large cells with multiple nuclei (figure 1B). It is my belief, not my conviction, that the levels of calcium and phosphate ions in the body fluids are held at such heights by the kidney, in its rôle of regulator of homeostasis, that dahlite is being constantly resorbed at bone-resorbing surfaces. The black arrows (figure 1B) indicate the passage of calcium from bone-resorbing surfaces (indicated by osteoclasts), to body fluids, to kidney, to outside world.

But bone formation and bone resorption occur at one and the same time. Where bone is being laid down one can see osteoblasts laying down uncalcified matrix (i.e. osteoid) and becoming enmeshed as osteocytes in this matrix. Obviously, there must be some local factor which favors the precipitation of the calcium-phosphate-carbonate salt, dahlite, at this point. It is highly probable that there is a localized increase in phosphate ions at bone forming surfaces due to the action of phosphatase or phosphorylase or both in splitting off inorganic phosphate from organic phosphate compounds (figure 1C).

As will be seen below, there are several factors which control the activity of the osteoblasts. However, the most fundamental stimulus is probably "stresses-and-strains" from without upon the skeleton. In this manner the skeleton adds to itself in order to withstand the stresses to which it is put. Furthermore, any surface on which the osteoblasts are building new matrix is insulated by this matrix from body fluids and hence will not be able to act as a bone-resorbing surface.

I will next introduce a series of arrows to indicate the movement of calcium in the body (figure 1D). These arrows speak for themselves. Note that the teeth have only ingoing arrows. One can *a*calcify a tooth but not *de*calcify it.

I will now introduce in the left lower quadrant of my synthetic man a structure to represent the steroid-producing endocrine glands (figure 1E).

These include the male and female gonads and the adrenal cortex. The steroid hormones (see small black arrows) circulate throughout the body and stimulate various structures. Of these, the most spectacular, if not the most vital, are the structures which constitute the secondary sexual characteristics and which give the body many of its contours. It will be noted in figure 1E that they also stimulate muscle growth, skin growth, and bone growth. One almost gets the impression that they stimulate all tissues. However, there is one interesting exception, the hair on top of one's head. This, as shown by Dr. James Hamilton, is inhibited by one of these steroids.

In figure 1F I will introduce a new wing to the structure representing the steroid-producing glands. Here steroid hormones of a different ilk are manufactured. They are represented by arrows with open heads. These steroids have an action opposite to that of the other steroids on certain of the tissues; thus, they inhibit, rather than stimulate, growth of these tissues. Their importance will be brought out later.

This, then, is a normal young man like you and me.

## The Aging Skeleton

Let us now contrast the bodily structures of our normal young man with those from an elderly individual, say a woman of 60 or a man of 80. The reason for the sex difference will appear shortly.

In examining the elderly individual (figure 2B) one is struck with how many of the changes can be explained on the basis of atrophy. Thus, his skin is thin and when pinched together forms waves with sharp crests as compared with the waves with rounded crests produced when the skin of a normal young man is similarly pinched (figure 2A); the muscle mass and the bone mass are likewise decreased. Moreover, the production of the steroid-producing glands is decreased. The axillary hair is scanty; certain secondary sex characteristics are less prominent than previously; et cetera, et cetera. The teeth are somewhat of an exception. To be sure, many have fallen out because of atrophy of the structure in which they were embedded or have been pulled out because of decay. The teeth which remain are not atrophied, albeit perchance riddled with caries.

Now let us examine the bone tissue more closely (figure 2B). It will be seen that the decrease in bone mass is due to a decrease in bone formation in the presence of a continued normal degree of bone destruction; in other words, the osteoblasts are not forming new bone matrix as rapidly as in our normal young man (figure 2A). The problem is one of decreased anabolism rather than increased catabolism. It seems probable that this same discrepancy is present in other tissues where we are not so fortunate as to be able to differentiate between decreased formation and increased destruction.

## Definition of Osteoporosis

To this form of bone disease where the disturbance is decreased production of osteoid by the osteoblasts is applied the term, "osteoporosis."

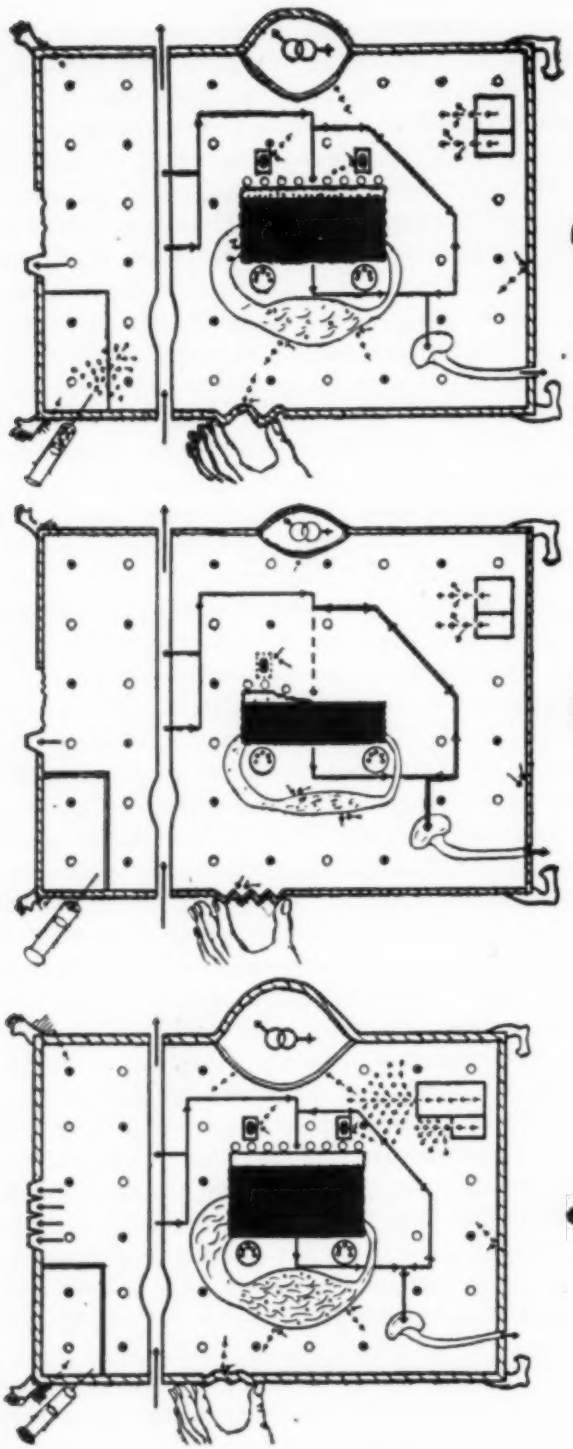


FIG. 2. Diagrams to illustrate senile osteoporosis and effect of steroid therapy.
(A) Normal young adult; (B) Senile individual; (C) Senile individual receiving steroid therapy.
For further discussion, see text.

The disorder is not primarily one of calcium-phosphorus metabolism but one of tissue metabolism; that bone matrix which is laid down is normally calcified. With continued bone destruction and decreased bone formation, the net result is a loss of calcium from the skeleton and hence an increase in calcium excretion in the urine. Osteoporosis is to be differentiated from two other conditions associated with too little calcified bone mass: osteomalacia, where there is a disturbance of the calcification of the osteoid, and osteitis fibrosa generalisata, where there is increased bone destruction.

## Ages of Entrances and Exits of Certain Steroidal Hormones

Since the steroids have so important a rôle in the problem at hand, let us examine the production of certain of these in relation to the age of the individual.

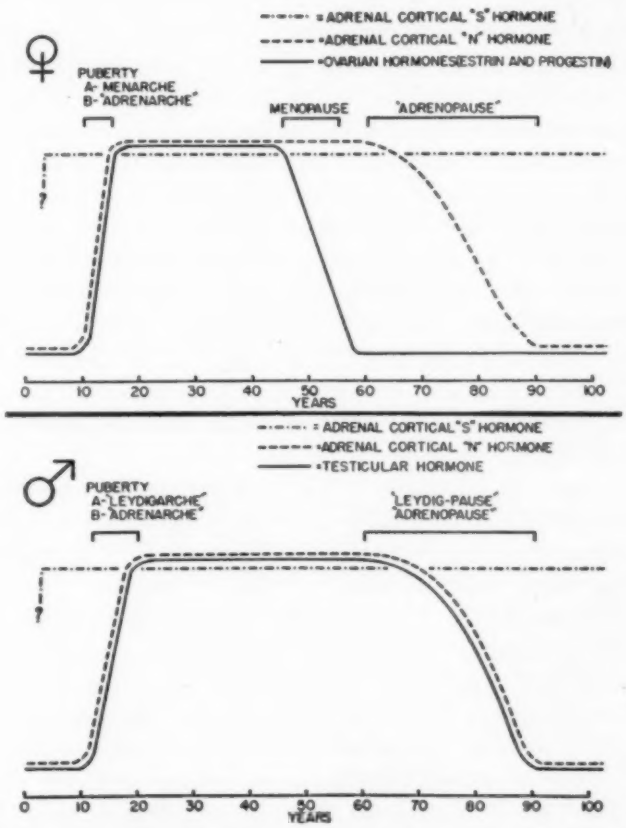


FIG. 3. Schematic diagrams for the female and the male to show their approximate ages at the times of entrance and exit of certain steroids on and off the scene.

In the female (figure 3) the ovarian hormones, estrin and progestin, are first produced in any quantity at the menarche. Their production falls rather precipitously at the menopause. Our knowledge concerning these

two hormones is facilitated by the fact that their presence is indicated by the menstrual cycle.

There is another key steroid hormone about which our knowledge also is quite clear. I speak of the adrenal cortical steroid hormone which has a somatotrophic action somewhat similar to the male gonadal hormone, testosterone, and the production of which in the female governs the growth of axillary and public hair and the excretion of 17-ketosteroids in the urine. I will call this hormone the adrenal cortical "nitrogen" or "N" hormone. The onset of its production is usually fairly synchronous with those of estrin and progestin and the manifestations produced by all three are usually attributed to one factor, namely, puberty. But in certain instances the onset of production of the "N" hormone is dissociated from the others. A patient with Addison's disease can have a normal menarche with regular periods, normal breast development, etc., but grow no axillary or pubic hair. Dr. Lawson Wilkins of Baltimore has told the speaker that he has seen a group of seven children in which the axillary and pubic hair production started very precociously whereas the menarche came at the usual time. Then, in the condition, ovarian agenesis, where the ovarian tissue is congenitally lacking, the production of axillary and pubic hair and of 17-ketosteroid precursors, in many instances, appears at the normal time for the menarche, albeit in reduced amounts for reasons which need not be discussed now.[6] In short, there is an "adrenarche"-with-respect-to-the-"N"-hormone without a menarche. The production of axillary and pubic hair and of 17-ketosteroid precursors continues after the menopause, from which I infer that the "adrenopause"-with-respect-to-the-"N"-hormone and the menopause are not simultaneous. None the less, there is an "adrenopause," as very elderly women have very scanty axillary and pubic hair and very low 17-ketosteroid excretions in the urine.

Now let us turn to the male. Since the androgens made by the interstitial cells of Leydig of the male gonads have an action similar in certain respects to that of the adrenal cortical "N" hormone, it is impossible as yet to draw a time-curve differentiating the two hormones. In other words, one cannot differentiate the "Leydigarche" from the "adrenarche." In all probability the gonadal hormones and the adrenal cortical "N" hormone start at the same time at puberty. They cease, not at the time of the female menopause, but probably at the time of the female "adrenopause" (figure 3).

In figure 1F it was pointed out that our normal young man possesses two types of steroids: one which stimulates anabolism and one which inhibits anabolism. The best and perhaps the only example of the latter type of steroid is the adrenal cortical "sugar" or "S" hormone. This is the hormone that promotes the breakdown of lymphoid tissue and thereby the release of immune globulin, that interferes with the burning of sugar by inhibiting the action of hexokinase, that facilitates deposition of glycogen in the liver; this is the hormone that in excess produces Cushing's syndrome, the hormone

that is most responsible for the manifestations of the adaptation syndrome of Selye,[9, 2] the hormone, the production of which by the adrenal cortex is under the control of the adrenocorticotrophic hormone (A.C.T.H.) of the pituitary; this is the steroidal hormone that has an oxygen on the 11th carbon atom and for which the "11-oxycorticosteroid" (11–OCS) determination of Talbot, Saltzman, Wixom, and Wolfe [10] is a quantitative expression. I do not know about infancy, but otherwise the production of "S" hormone is present throughout life (figure 3). Its property of antianabolism may be due to some disturbance in building amino acids into protoplasm or to a shortage of amino acids because of their increased conversion into glycogen in the liver, or to any one of a dozen other possibilities.

## Steroidal Inbalances as Causes of Osteoporosis

1. Old Age. In looking for the cause of the atrophy of multiple tissues in our elderly individual (vide supra) the question arises whether atrophy of those glands producing anabolic steroids occurs first, and leads secondarily to atrophy of other organs, or whether old age per se causes atrophy of all tissues. This question can be put to the test. If the atrophy is secondary to decrease in steroid production, it should respond to steroid therapy (figure 2C). It does, at least to a certain degree. We have shown that testosterone propionate stimulates protoplasmic anabolism with retentions of nitrogen, phosphorus, potassium, and sulfur in the proportions in which they are found in protoplasm (figure 4); but, what is more pertinent to the present discussion, the atrophy of bone which occurs in old age is offset by the administration of estrogens and/or androgens (figure 5).

*The first cause of osteoporosis on a steroidal basis, therefore, is old age with its atrophy of bone as one of multiple tissues; this atrophy is at least partly attributable to decreased production of anabolic steroids in the presence of continued production of anti-anabolic steroids.*

2. The Post-Menopausal State. From the discussion above it is seen that senility is ushered in by a puberty in reverse. It is further seen that there are at least two steps in the turning-off of steroid production in the female, the menopause and the "adrenopause." Since estrin has a marked effect in stimulating osteoblasts (figure 6), the first of these steps is followed by osteoporosis. The relatively early onset of the menopause accounts for the fact that osteoporosis is so much more common in females.

*A second etiology for osteoporosis on a steroidal basis, therefore, is the post-menopausal state where the cause is a lack of estrin production.*

3. Cushing's Syndrome; Adaptation Syndrome of Selye; Administration of Adrenocorticotrophic Hormone (A.C.T.H.). I have mentioned two conditions where osteoporosis is due to lack of anabolic steroids; essentially the same situation can be brought about by an excess of the anti-anabolic-adrenal-cortical "S" steroid such as one meets in Cushing's syndrome and during the stage of resistance of the adaptation syndrome of Selye or after the administration of A.C.T.H.

In figure 7B the speaker's interpretation of the pathological physiology of certain aspects of the adaptation syndrome and of Cushing's syndrome is shown diagrammatically. Until recently I have felt that the modus operandi of testosterone in offsetting this disordered physiology was by virtue of

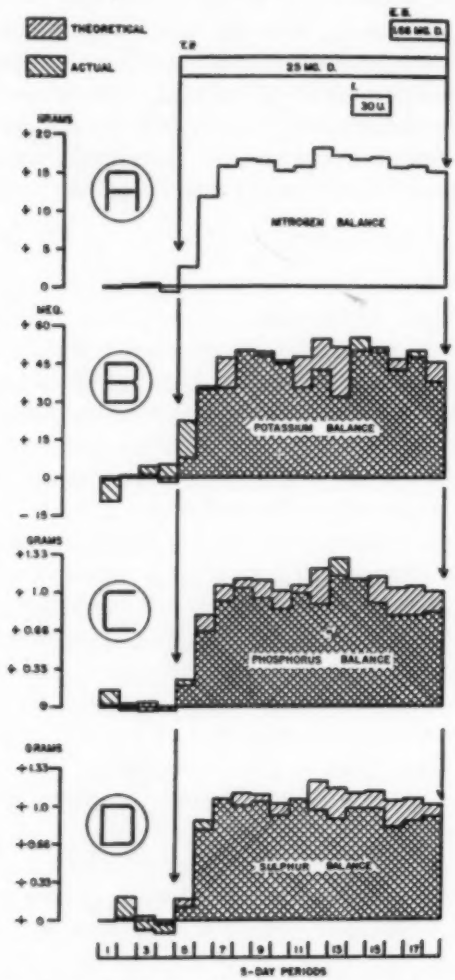


FIG. 4. A comparison of deviations in the nitrogen balance with those of the potassium, phosphorus, and sulfur balances as a result of testosterone propionate therapy in a patient with Cushing's syndrome (B.V., No. 74372).

The balances are charted as deviations from the averages of the four control periods. T.P. = testosterone propionate; I. = insulin; E.B. = estradiol benzoate; D. = dosage per day; U. = units per day. The data for potassium are based on analyses of urinary excretion alone.

The chart has four divisions: A = the measured nitrogen balance; B = the measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the potassium balance; C = measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the phosphorus balance (after the phosphorus theoretically retained with calcium had been subtracted); D = measured nitrogen balance superimposed on the theoretical nitrogen balance explainable by the measured sulfur balance. This study has been published elsewhere in more detail.[4, 6]

overcoming an anti-anabolic effect by the introduction of an anabolic effect. A second possibility will be discussed below.

In figure 8 the effect of testosterone propionate therapy in reducing the calcium excretion in a female patient with Cushing's syndrome is illustrated.

It is probably premature to discuss the action of A.C.T.H. since this substance has been available a short time only and the observations require checking. Since A.C.T.H. presumably releases "S" hormone from the

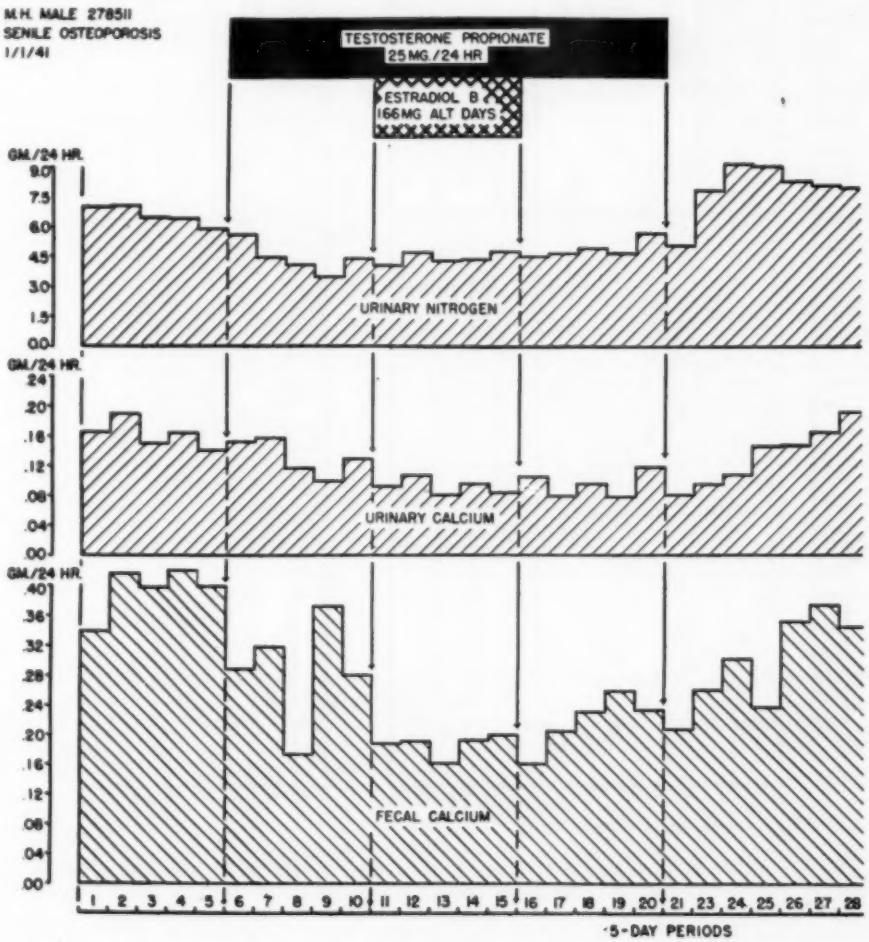


FIG. 5. Effect of testosterone propionate alone and in combination with estradiol benzoate on urinary nitrogen excretions and on urinary and fecal calcium excretions of a patient with senile osteoporosis.

The patient (M.H., No. 278511) was on a constant intake throughout the 28 five-day periods. Note the marked reduction in nitrogen excretion on the administration of testosterone propionate and the rebound when testosterone propionate was omitted; and that estradiol benzoate had no effect on the nitrogen excretion. Note that testosterone propionate reduced both the fecal and urinary calcium excretions and that estradiol benzoate further reduced both of the excretions. A more complete discussion of this study will be found elsewhere.[5]

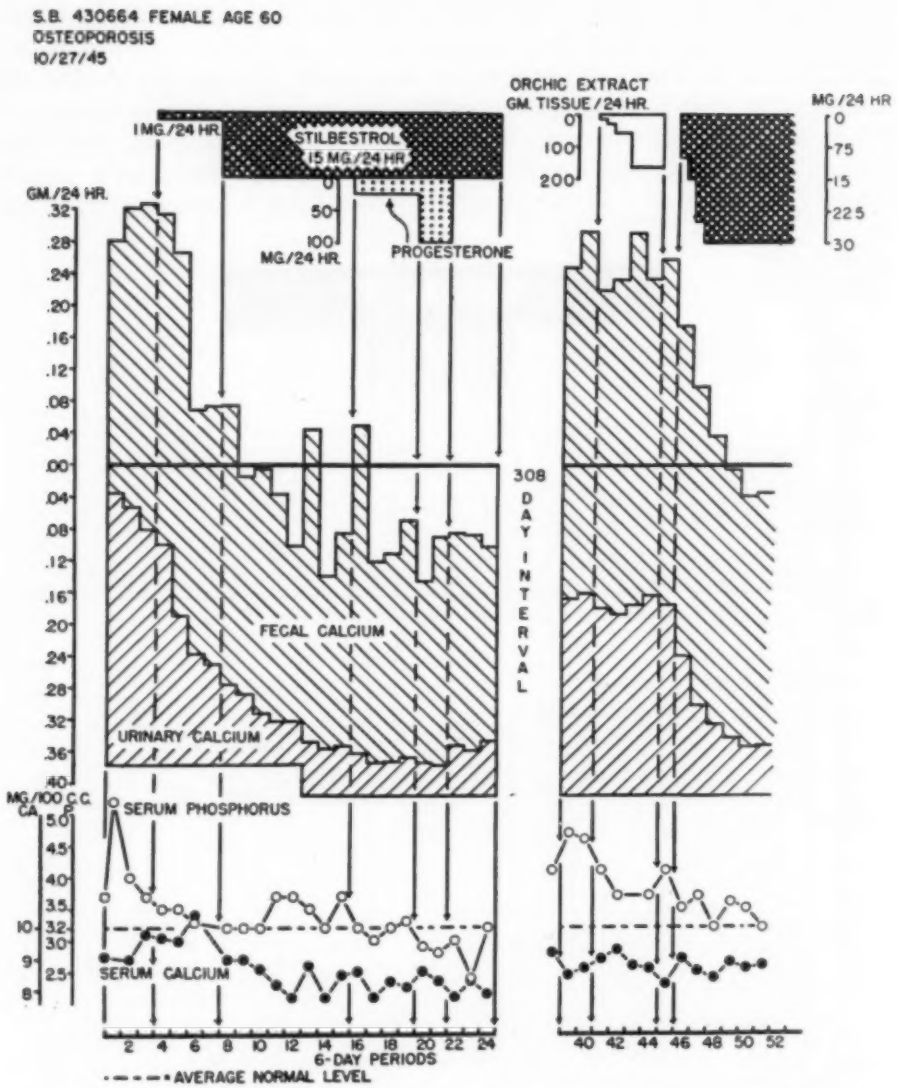


FIG. 6. Effect of diethylstilbestrol at various dose levels on calcium metabolism of a patient with post-menopausal osteoporosis complicated by Paget's disease.

Metabolic data in this figure are arranged according to the following scheme. There is a horizontal base line; intake is charted on a reverse scale downward from this base line; urinary and fecal excretions are measured from the intake line upward toward the base line; thus, a positive balance is indicated by a clear area below the base line; a negative balance by a hatched area above the base line.

Note marked fall in urinary calcium excretion with diethylstilbestrol; note, furthermore, that 30 milligrams daily is not much more effective than one milligram daily (compare metabolic periods 4 through 7 with periods 46 through 49). Note that serum phosphorus level tends to fall on therapy; that the addition of progesterone to the diethylstilbestrol medication (periods 16 through 21) had no marked effect. The "orchic extract" given in periods 41 through 44 was apparently without effect and need not be discussed further here. For more detailed discussion of the first 24 six-day metabolic periods see a previous publication.[5]

adrenal cortex, with a potent preparation of A.C.T.H. one is in position to study the initial effect of "S" hormone. By the time one sees a patient with Cushing's syndrome secondary changes have set in and one cannot tell which is the cart and which is the horse. The quantity of "S" hormone, itself, available is too small to allow decent metabolic studies on human beings.

In figure 9 the effect of A.C.T.H. on a male patient, 41 years of age, suffering from mild panhypopituitarism (chromophobe pituitary adenoma) is shown.* It will be noted that with A.C.T.H. administration there was a marked but poorly sustained rise in nitrogen, phosphorus, and potassium

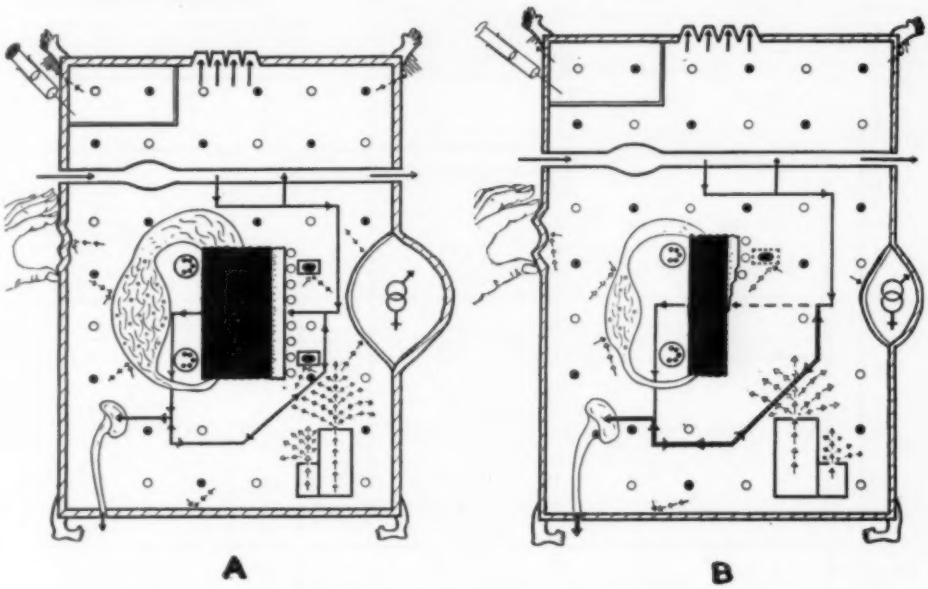


FIG. 7. Schematic diagram to compare pathological physiology of Cushing's syndrome and adaptation syndrome of Selye (B) with the normal (A).
The decrease in the production of anabolic steroids depicted in this figure is more compatible with the adaptation syndrome than with Cushing's syndrome; both syndromes have in common the over-production of the anti-anabolic steroid.

excretions. The same was true of the 11-oxysteroid and 17-ketosteroid excretions which are not charted. Directly concerned with the present discussion, however, is the striking rise in the urinary calcium excretion which was better sustained than that of the other substances measured. Moreover, during the second course of A.C.T.H. administration (period 10), when there was no rise in nitrogen excretion, there was a definite increase in calcium excretion.

*A third cause for osteoporosis on a steroidal basis, therefore, is the group of conditions—Cushing's syndrome, adaptation syndrome of Selye, and the*

* The A.C.T.H. for this experiment was supplied by Dr. John Mote of the Armour Company. These studies were carried out in conjunction with Dr. Frederic Bartter and Dr. Anne P. Forbes.

*patient receiving A.C.T.H.: in the triad the one common denominator is an over-production of adrenal-cortical "S" hormone.*

From the above discussion it is seen that there are three steroidal hormones stimulating the osteoblasts (adrenal cortical "N" hormone, estrogen, and testosterone) and one steroidal hormone inhibiting the osteoblasts (adrenal cortical "S" hormone). In the normal female and normal male these hormones are in balance (figure 10); in the post-menopausal state, old

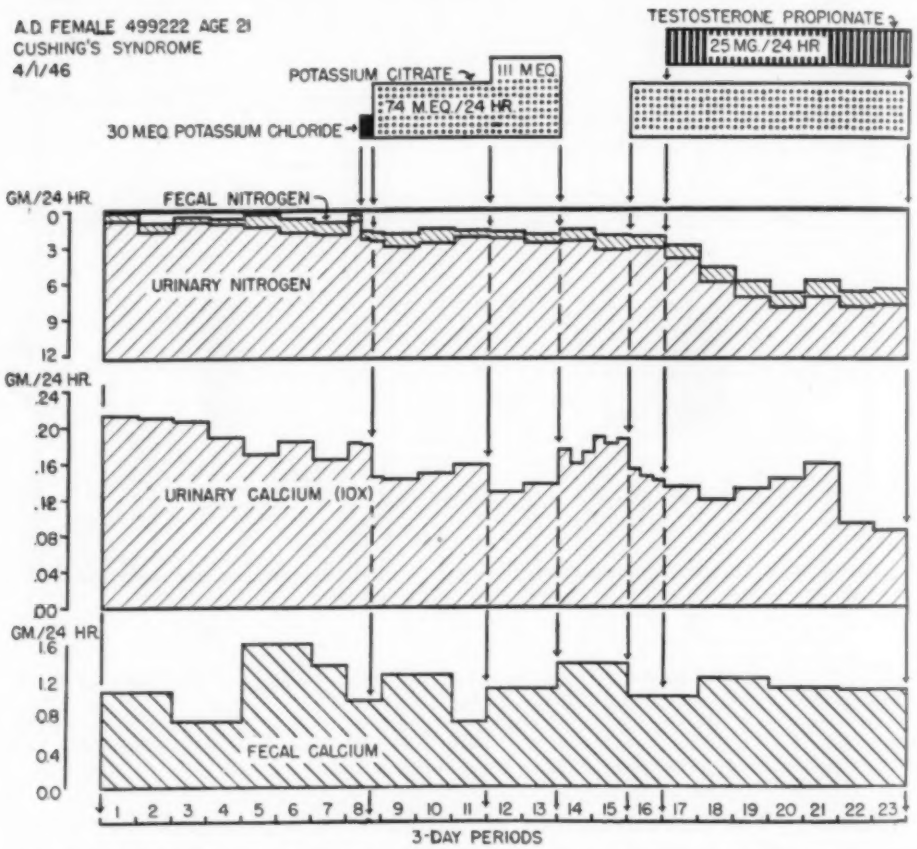


FIG. 8. Metabolic study to show effect of testosterone propionate in decreasing calcium excretion in a patient with Cushing's syndrome.

The study entailed 23 three-day periods on a constant intake. Selected for this figure are the nitrogen metabolic data and the urinary and fecal calcium excretions. The nitrogen metabolic data are charted according to the scheme outlined in the legend to figure 6. Note the marked fall in the urinary nitrogen and calcium excretions during testosterone propionate therapy (periods 17 through 23). Attention might be called—although no further comments on it will be made—to the definite decrease in the urinary calcium excretion and the suggestive decrease in the urinary nitrogen excretion with an increase in potassium intake.

This study was carried out on patient A.D., No. 499222, aged 21, with classical Cushing's syndrome resulting from adrenal cortical hyperplasia as shown by operation (see also figure 11); the data have not yet been published; they were collected in conjunction with Dr. Edward C. Reifenstein, Jr., Dr. Frederic C. Bartter, and Dr. Anne P. Forbes, and it is anticipated that the complete study will be published later in conjunction with these colleagues.

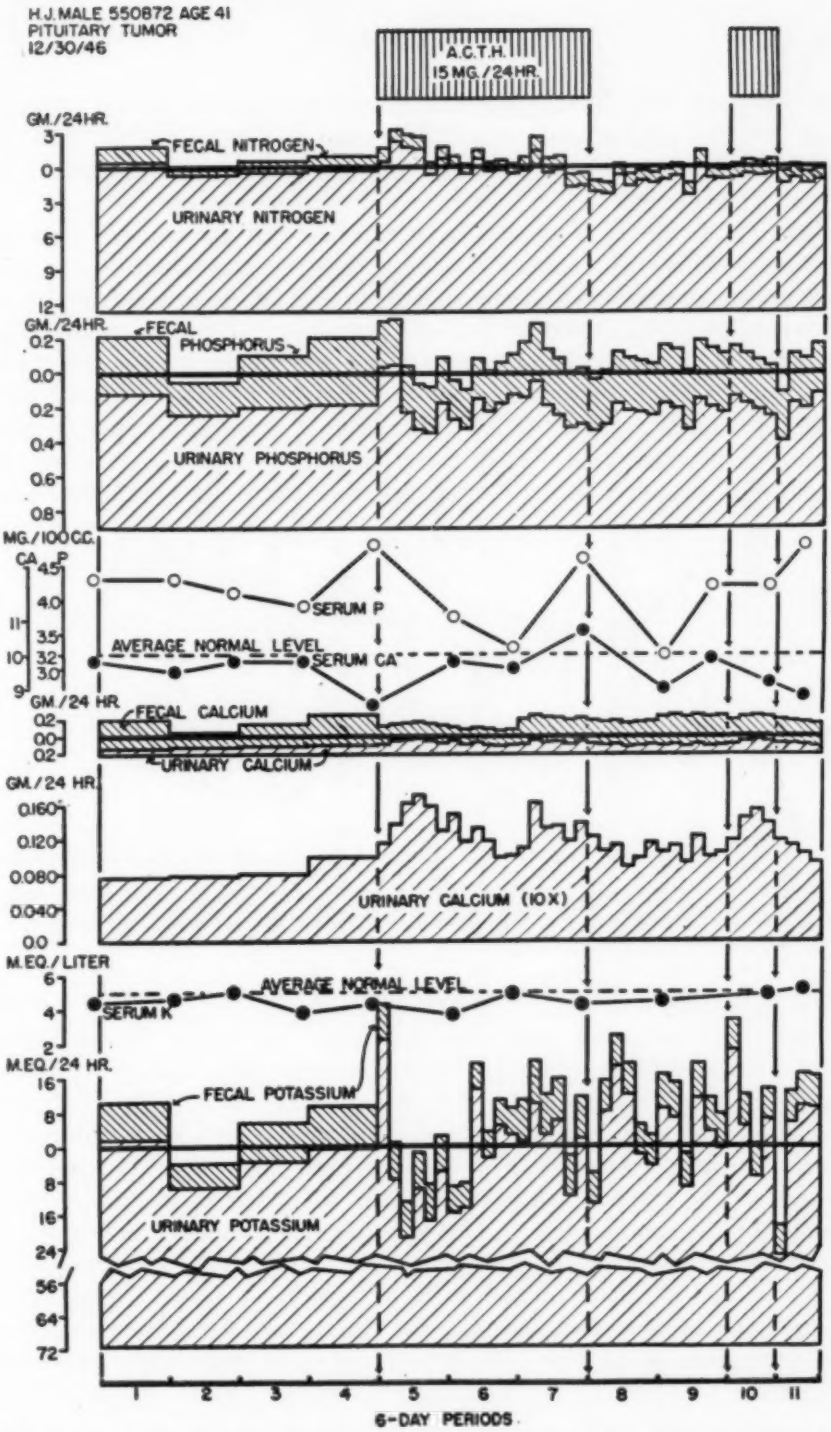


FIG. 9. Metabolic study showing effect of A.C.T.H. on a patient with panhypopituitarism secondary to a chromophobe adenoma.

Charted are the nitrogen, phosphorus, calcium, and potassium metabolisms; the serum phosphorus, calcium, and potassium levels; and a magnified version of the urinary calcium excretion by itself. For further discussion, see text. It is anticipated that the complete study will be published in the near future.

age in either sex, and Cushing's syndrome these hormones are out of balance (figure 10) and osteoporosis results; in panhypopituitarism the hormones are all markedly reduced but the balance is maintained so osteoporosis does not result (figure 10).

*Mode of Action of Testosterone Propionate in Causing Protoplasmic Anabolism.* There is abundant evidence that the administration of testosterone propionate promotes tissue anabolism. It has been assumed that this is a direct stimulating action on anabolic processes. Thus, testosterone promotes growth in the combs of capons when administered topically. There may, however, be another mechanism. It has been shown in Dr. Edward Dempsey's laboratory that the administration of testosterone propionate to rats leads to decreased steroids in their cortices.* Venning and Browne [12] found a fall in the adrenal cortical "S" hormone excretion (biological assay)

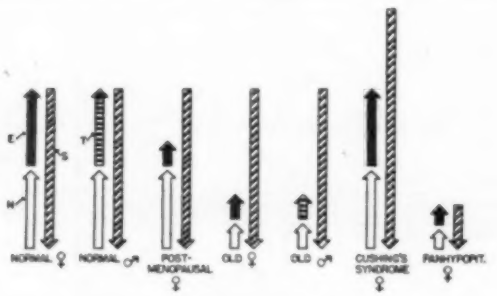


FIG. 10. Schematic diagram to show effect of certain steroidal hormones on osteoblastic activity.

E. = estrogen; N. = adrenal cortical "N" hormone; S. = adrenal cortical "S" hormone; T. = testosterone. An arrow pointing upward represents a stimulating effect; an arrow pointing downward represents an inhibiting effect. For further discussion, see text.

following the administration of testosterone propionate. Talbot, Albright, Saltzman, Zygmuntowicz and Wixom [13] have reported a fall in 11–OCS excretion following administration of testosterone propionate.

In figure 11 are shown on a female patient of 21 with Cushing's syndrome the effect on the 11–OCS and 17–KS excretions of a high-protein diet, added potassium citrate, testosterone propionate, and two adrenal explorations. Pertinent to the present discussion are the following observations on this patient: (1) the marked fall in 11–OCS excretion under administration of testosterone propionate (see days 86 through 107), (2) the failure of the 11–OCS excretion to rise following the first operation when the patient had been receiving testosterone, and, (3) the rise in 11–OCS excretion after the second operation when the patient had not been receiving testosterone.† Dr. Edward Dempsey reported that both adrenal cortical biopsies showed

*The steroids are studied for three properties: (1) birefringence, (2) reaction to Schiff's stain, and (3) reaction to Sudan stain.

†A rise in 11–OCS excretion following trauma and hence following an operation is the expected finding; the rise is increased in patients with Cushing's syndrome.

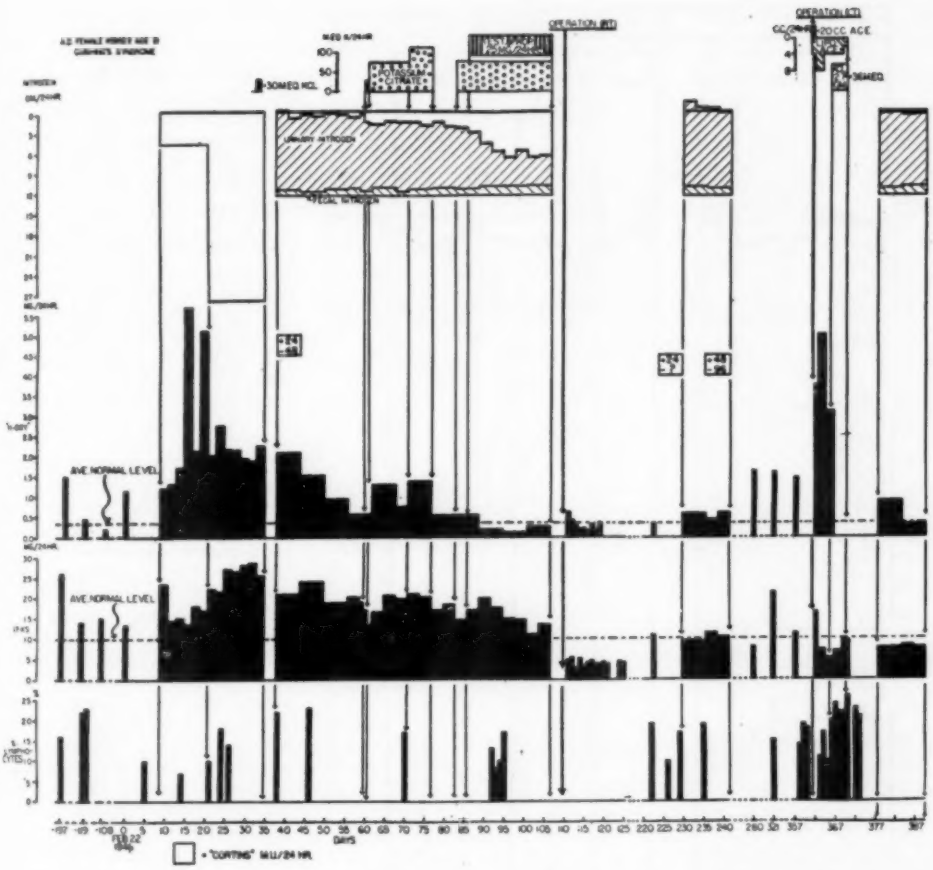


FIG. 11. Study on a patient with Cushing's syndrome to show effect of various procedures, notably administration of testosterone propionate, on the 11-oxycorticosteroid and 17-ketosteroid excretions and the percentage of lymphocytes in the blood smear.

The figure includes the nitrogen intake by itself from day 8 to day 35, the total nitrogen metabolism (urine, feces, and intake) from day 37 to day 107, from day 228 to day 240, and from day 377 to day 389. Data presented in figure 8 are derived from the same study and represented days 37 to 107.

Of special concern to the present discussion are the 11-oxycorticosteroid excretions. Note that, in spite of wide fluctuations, they tend to be high throughout, that they fall to the normal range with testosterone therapy, that there is virtually no rise following the first adrenal exploration (day 110), but that there is a marked rise following the second operation (day 361); note in this connection that the patient was receiving testosterone propionate up to the first operation, but not before the second operation. For further discussion of 11-oxycorticosteroid excretions in this case, see text.

There are also included in the figure the results of three assays of 11-oxycorticosteroids by the biological method. All three values are high, the normal individual being positive for three and negative for 24 mouse units per day.

The 17-ketosteroid excretion and the percentage of lymphocytes in the smear do not particularly concern the present discussion. It should be pointed out, however, that, with the administration of testosterone propionate, the 17-ketosteroid excretion does not rise; this indicates that its endogenous production in the adrenal cortex is decreased sufficiently to offset the increase from the exogenous source.

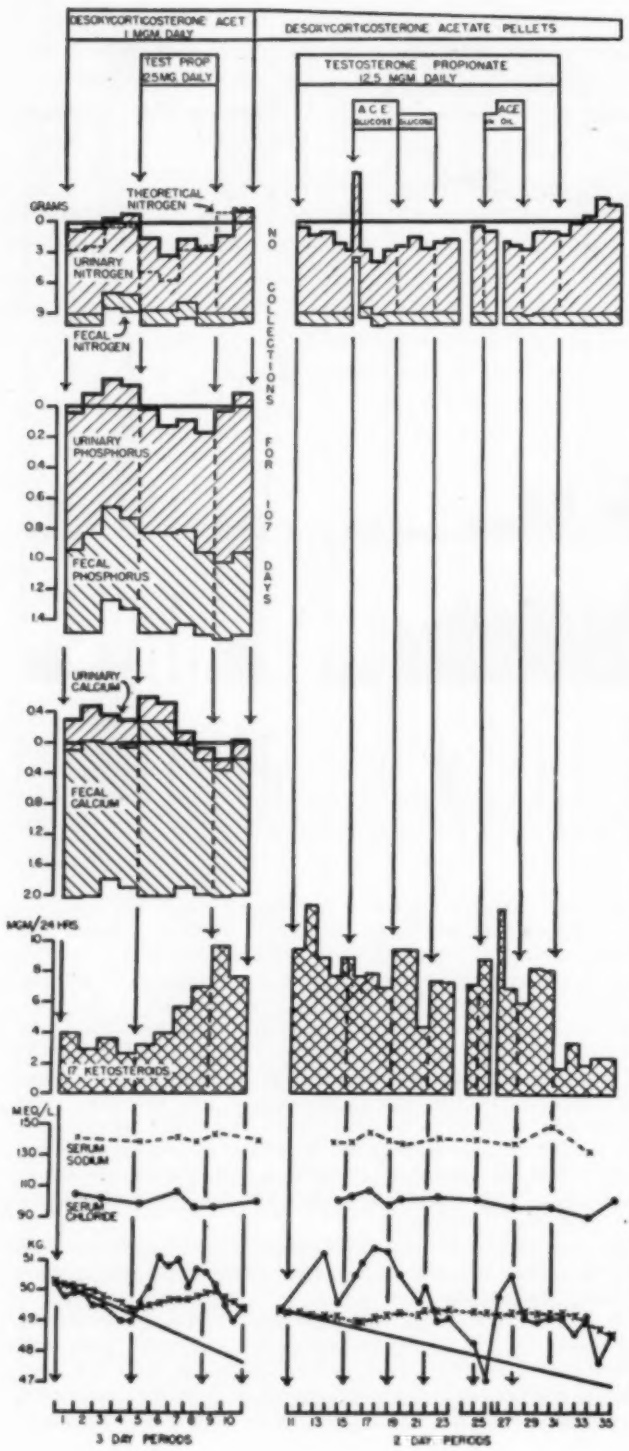


FIG. 12. Metabolic study on patient with Addison's disease to show that testosterone propionate can exert its somatotrophic action in the absence of the adrenal cortex.

The study is divided into two parts with an interval of 107 days. The first part consists of 10 three-day metabolic periods, the second of 25 two-day metabolic periods. During the first part of the study the patient received desoxycorticosterone acetate, one milligram daily intramuscularly; before the second part of the study she had been implanted with desoxycorticosterone acetate pellets. The nitrogen, phosphorus, and calcium metabolic data are arranged according to the scheme used in figure 6. A.C.E. = adrenal cortical extract.

Note the decrease in nitrogen (both parts of the experiment), phosphorus, and calcium excretions on the administration of testosterone propionate and the rebound in the excretions when this substance was omitted. The unexpectedly high 17-ketosteroid excretion (circa three milligrams per day) for a female patient with Addison's disease is to be explained by an interfering, non-specific ketone. This value was wiped out when the extract was put through Girard's reagent. The weight curves at the bottom of the figure do not concern the present discussion. The curve connecting black circles represents the actual weight. The curve connecting "X's" represents the "theoretical-weight-based-on-nitrogen." [8]

The data shown in this figure pertain to patient S.G., No. 385496, and were collected in conjunction with Dr. Edward C. Reifenstein, Jr., Dr. Laurence Kinsell, and Dr. Anne P. Forbes.

hyperplasia but that the first biopsy showed the zona fasciculata devoid of the cortical steroids, whereas the second biopsy showed this tissue filled with steroids. It would appear that testosterone therapy depleted the cortices of steroids, thus lowering the 11–OCS excretion and making impossible a post-operative release of said hormone. To be sure, the patient received Upjohn's lipo-adreno-cortical extract following the second operation, but it is very unlikely that this could account for the high value of 11–OCS excretion at that time (figure 11).

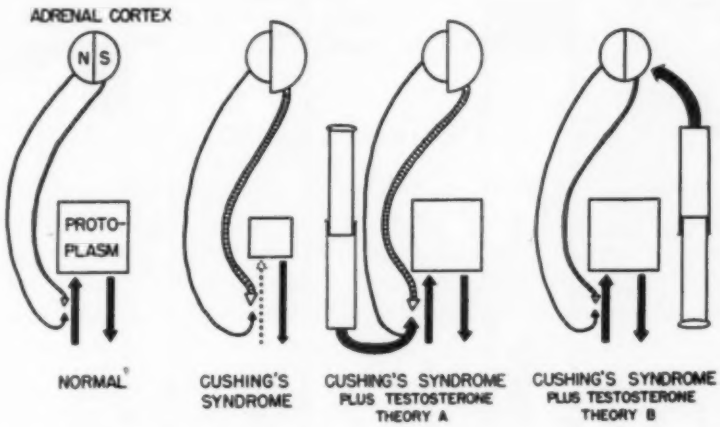


FIG. 13. Schematic diagrams to illustrate two of the possible actions of testosterone on protoplasm.

Note in the normal individual that protoplasm is being built up and broken down; that the adrenal cortical "N" hormone stimulates the anabolism of protoplasm and the adrenal cortical "S" hormone inhibits this action. Note in Cushing's syndrome that there is an excess of adrenal cortical "S" hormone and hence an inhibition of the anabolism of protoplasm. Note in Cushing's syndrome, when testosterone is administered by a syringe, that according to theory A it balances the inhibiting action of adrenal cortical "S" hormone and hence allows the normal anabolism of protoplasm; that according to theory B it inhibits production of adrenal cortical "S" hormone and hence allows the normal anabolism of protoplasm.

The above observations, by themselves, suggest that testosterone propionate affects protoplasm by inhibiting production of the anti-anabolic adrenal cortical "S" hormone. That this cannot be its only effect on protoplasm is shown by the fact that it causes nitrogen and phosphorus retention when administered to an individual devoid of adrenal cortical tissue—i.e. a patient with Addison's disease (figure 12). Thus, whether testosterone has a direct stimulating effect on anabolism of protoplasm, or whether it inhibits production of the antianabolic "S" hormone, or whether it does both these things, we must for the time being reserve judgment. In figure 13 are shown in schematic fashion the two manners in which testosterone may exert its effect on protoplasm.

*Stress-and-Strain Factor in Osteoporosis.* As mentioned above, the most fundamental stimulus for an osteoblast is the feeling on its part that the

skeleton is unstable. It follows that an osteoblast will stop producing if the skeleton is put at rest by being immobilized in a plaster cast [7] or by virtue of paralysis of the muscles pulling on the skeleton. This aspect of the subject is so self-evident that it is only mentioned here for completeness' sake. Osteoporosis from other causes often leads to a superimposed disuse atrophy which may be unavoidable, but which is often abetted by over-fixation on the part of the orthopedic surgeon. Disuse atrophy is also a factor in the osteoporosis of old age.

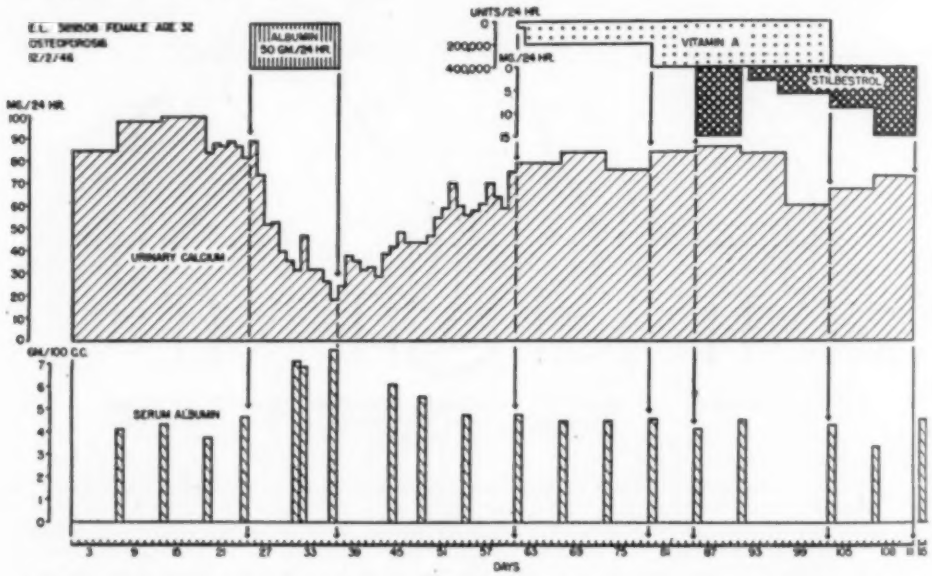


FIG. 14. Metabolic study on a patient with idiopathic osteoporosis to show the inverse relationship between the height of the serum albumin level and the urinary calcium excretion. Shown in the figure are 111 consecutive days during which the patient was on a constant dietary regimen. From day 25 through day 36 she received approximately 50 grams of purified serum albumin * per day.

*Lack of Nitrogenous Building Blocks as a Cause of Osteoporosis.* It is obvious that the osteoblasts could be stimulated by a maximum of stresses and strains and by an optimal mixture of the anabolic steroids and still be incapable of producing bone matrix if the necessary nitrogenous building blocks were not available. Osteoporosis is a common finding in starvation and malnutrition. There is considerable circumstantial evidence that serum albumin may be one of the important building blocks. Severe osteoporosis is met in nephrosis.[14] We have studied two patients with idiopathic osteoporosis in whom the osteoporosis was made much worse by pregnancy, a condition in which the serum albumin is low; in one of these two patients a

* The purified albumin preparation used in this study was made available to us by Dr. Edwin J. Cohn and Dr. Charles A. Janeway.

Note that vitamin A had no effect on the urinary calcium excretion and that diethylstilbestrol had a minimal effect, if any.

For further discussion, see text. This study will be published in detail elsewhere.[14]

therapeutic abortion was followed by a rise in the serum albumin level and a decrease in the negative calcium balance. With these observations in mind, we carried out a metabolic experiment with serum albumin on this same patient. The data are shown in figure 14. It will be seen that she received approximately 50 grams of purified serum albumin daily for 12 days while on a constant metabolic regimen. It will be noted that her urinary calcium excretion bore an inverse relationship to her serum albumin level. In a second experiment the same procedure was carried out except that the albumin was given by mouth rather than by vein; there was no fall in the urinary calcium excretion.

*It is concluded that serum albumin is one of the important nitrogenous precursors of bone matrix.*

## Summary and Preliminary Conclusions

1. Osteoporosis is defined as that category of decreased bone mass where the disturbance is a failure of the osteoblasts to lay down bone matrix.

2. Three factors which influence osteoblastic activity are discussed: (a) steroidal hormones, (b) mechanical stresses and strains, and (c) nitrogenous building blocks.

3. In respect to bone matrix, the steroids can be divided into anabolic steroids (estrogens and androgens), anti-anabolic steroids (adrenal cortical "S" hormones), and anabolically-inert steroids (progesterone).

4. The age of entrance of adrenal cortical "N" hormone on the scene is termed the "adrenarche"; the age of exit, the "adrenopause." The adrenarche is usually synchronous with the menarche; the adrenopause is normally considerably later than the menopause. The adrenal cortical "S" hormone is produced at the same level during childhood, age of sexual maturity, and senility.

5. The osteoporosis of old age is partly to be attributed to the loss of gonadal hormones and of the adrenal-cortical "N" hormone and responds to estrogen and testosterone therapy.

6. The osteoporosis of the post-menopausal state is to be attributed to the decrease in estrogen production following the menopause and responds to estrin and testosterone therapy.

7. The osteoporosis in Cushing's syndrome and in the adaptation syndrome of Selye is to be attributed to an excess of the anti-anabolic adrenal cortical "S" hormone and responds to testosterone therapy.

8. The adrenocorticotrophic hormone, by releasing "S" hormone from the adrenal cortices, likewise produces osteoporosis; the effect of A.C.T.H. on panhypopituitarism is demonstrated.

9. Evidence is presented to suggest that the effect of testosterone in stimulating anabolism may be partly, but probably not wholly, due to its property of causing decreased production of the adrenal cortical antianabolic "S" hormone rather than entirely to a direct anabolic property of its own.

10. The production of bone matrix is undoubtedly influenced by the availability of certain nitrogenous substances; evidence is presented which suggests that the height of the serum albumin is an important factor.

## Concluding Remarks

1. I have told you more about osteoporosis than I know.
2. What I have told you is subject to change without notice.
3. I hope I have raised more questions than I have given answers.
4. In any case, as usual, a lot more work is necessary.

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# OBESITY *

By CLIFFORD F. GASTINEAU, M.D., and EDWARD H. RYNEARSON, M.D., F.A.C.P., *Rochester, Minnesota*

ALTHOUGH the dangers and handicaps imposed by obesity have been enumerated by many writers, the seriousness of this disease is not fully appreciated. It is easy to shrug off "a few pounds of overweight" as something of little consequence, but in doing so the physician is ignoring what is perhaps his best chance to lengthen the life and diminish future illnesses of his patient. Statisticians have pointed out the increase in deaths from the degenerative diseases such as cancer, diabetes and heart disease,[1] and the implication has been that medicine is approaching a point of diminishing returns, that increasing efforts will reduce the death and illness rates only slightly. Actually, a great improvement in the health of the nation appears possible by means of the correction and prevention of obesity. Statistical studies have demonstrated the association of obesity with hypertension,[2, 3] pulmonary emphysema,[4] diabetes,[5] heart disease,[2] cancer,[6] acute and chronic nephritis,[2, 7] cirrhosis,[7] accidents [7] and atherosclerosis.[8]

These studies suggest that by the treatment of obesity the physician may ameliorate considerably the effects of many diseases for which otherwise he has little specific treatment. The increased dangers of surgical treatment [9] and pregnancy [10] in the presence of obesity, the greater severity of degenerative arthritis in the knees, hips and lumbar spine of the obese,[11] the increased incidence of gall-bladder disease [9] and the earlier appearance of varicose veins [11] are further reasons for the correction of obesity.

A statement which may impress the doubtful patient with the urgency for weight reduction is: "Between the ages of 45 and 55, 25 pounds of excess weight means a 25 per cent greater chance of dying within the next year; 50 pounds of overweight means that you have a 50 per cent greater chance of death in the next year than the person of normal weight." [12]

While there is no question but that obesity increases the incidence of a large number of pathologic processes, it cannot be assumed with such certainty that the reduction of the weight of an obese person to normal will give him health equivalent to that of the person who has never been obese. Some of the changes caused by obesity, such as emphysema,[4] tend to become irreversible in time, but others may be corrected by weight reduction.[3] It seems reasonable to assume that the shorter the duration and the less the degree of the obesity, the more easily will normal health expectancy be restored. It is, therefore, as important to prevent as to correct obesity.

* Read at the meeting of the American College of Physicians, Chicago, Illinois, May 2, 1947.

Dr. Gastineau is Fellow in Medicine, Mayo Foundation and Dr. Rynearson is Consultant in Medicine, Mayo Clinic and Associate Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.

Aside from the reasons mentioned, there are serious psychologic problems stemming from obesity. Marked obesity is essentially a repulsive disease, and its victim tends to feel rejected, unable to join with others in many of the ordinary activities with complete acceptance. Because physical activity requires greater effort for the obese, the victim is likely to retreat to a state of inactivity and thereby perpetuate and accentuate the condition. The frequent occurrence of neuroses in the obese has been emphasized by several investigators.[13-17] It should be pointed out, however, that similar psychologic investigations of control groups of nonobese persons might have revealed a similar incidence and variety of neuroses. It is of course difficult to judge, also, what proportion of psychologic changes is the result of and how much is the cause for the obesity. Esthetic reasons for the treatment of obesity are not the least important. The desire to be attractive is possibly the most frequent reason that the overweight person goes to the physician for help in reduction of weight.

In consideration of all these factors, it would seem desirable that more doctors develop something of the missionary spirit and zeal in correcting obesity.

## Physiology

Early in the investigations of obesity, several cases were reported in which there appeared to be a maintenance of obesity in spite of low caloric intakes.[18, 19] These findings seemed to confirm the popular idea that there are fat people who stay fat no matter how little they eat.[20] However, in more recent and better controlled studies it has been shown that obese persons must eat more than the average person in order to remain obese.[18, 21-24] This statement has been made previously in many forms and for emphasis it is here repeated: *Fat comes only from food, and obesity results only from eating more than is required to meet the energy requirements of the body.*[25, 26] There are many capable investigators, however, who believe that there are those with a tendency toward leanness who can overeat with impunity, and there are those with a predisposition to obesity who will become stout although eating no greater amount.[20, 27] It is felt by these investigators that some obese persons have an unusual mechanism for conserving energy not possessed by other people. It is sufficient to say that such a mechanism has never been adequately demonstrated,[12, 23] and the very multiplicity of suggested abnormalities of metabolism argues against such a possibility.

There are a number of devices which appear to regulate body weight. Perhaps the most important is the appetite mechanism. No one has been able to explain satisfactorily what determines satiation, but it probably depends upon the interaction of a number of factors.[28] The striking effect of hypothalamic damage in producing obesity through increased appetite [29] suggests that an important center for normal appetite regulation may reside

there. The importance of psychic conflict in the development of obesity in persons exhibiting compulsive eating has frequently been observed, thus demonstrating that the cerebral cortex may override the more automatic and primitive appetite control centers.

It is the familiar plaint of the fat person that "I don't eat a thing and I still get fat." It has been well proved that such a person does eat excessively,[22, 24] and it is interesting to speculate why this belief should so frequently arise. A possible explanation is that the person with the predisposition to obesity has an appetite mechanism (whatever that may consist of) which requires a larger than normal amount of food before satiation is accomplished. If he eats what would satisfy the normal person he remains hungry and feels that he has eaten very little; if he eats anything less than what is required for satiation he is likely to believe honestly that he has eaten little, even though he has consumed large quantities of food. A corresponding situation appears to exist for the person with a tendency toward leanness.

Another device for regulation of body weight is the association of energy requirement with the surface area.[22, 23, 25, 30] It has been shown that the number of calories required by the body at resting state is proportional to the surface area. Thus a 35 year old man, 5 feet and 7 inches (170 cm.) tall with a surface area of 1.79 square meters will maintain a normal weight of 150 pounds (68 kg.) with an intake of 2,415 calories each 24 hours (table 1).

TABLE I

Varying Food Requirements for a 35 Year Old Man at Different Body Weights *

| Weight, Pounds | Surface Area, Square Meters | Calories Required per 24 Hours | |
|---|---|---|---|
| | | At Basal Conditions | With Moderate Activity† |
| 100 | 1.50 | 1,360 | 2,040 |
| 150 | 1.79 | 1,610 | 2,415 |
| 200 | 2.02 | 1,840 | 2,760 |
| 250 | 2.22 | 2,020 | 3,030 |
| 300 | 2.40 | 2,170 | 3,255 |

* These calculations assume a basal metabolic rate of 0 and were obtained by use of the Boothby-Berkson nomogram for a 35 year old man 5 feet and 7 inches tall who had a standard weight of 150 pounds.

† Caloric requirements at moderate activity are assumed to be 50 per cent greater than those at basal conditions.

If he consumes 3,255 calories (34 per cent more) he will gradually gain in weight until he reaches 300 pounds (136 kg.) and a surface area of 2.4 square meters (34 per cent greater). The weight gain of such a man weighing 150 pounds and eating 3,255 calories will at first be 1.7 pounds (0.8 kg.) per week. The rate of gain will gradually become slower until it ceases at 300 pounds. Similarly if this same man weighed 300 pounds and were fed 2,415 calories daily he would lose 1.7 pounds a week at first, the rate of loss gradually slowing as his weight approached 150 pounds. From

these figures * it can be seen that a small daily excess of food does not lead to unlimited gains in weight as once postulated by von Noorden,[19] but rather to definite, calculable and limited increases. This removes some of the mystery with which the appetite mechanism was surrounded when von Noorden pictured it as a device of almost incredible accuracy. It also diminishes the necessity for postulating obscure aberrations in energy metabolism which would adjust energy output to fit the intake.

Another phenomenon which aids in the regulating of weight is the fall in the basal metabolic rate with decreased intake of food. After several weeks on a reduced diet, there is often, but not invariably [18, 32] a decrease in the basal metabolic rate. This phenomenon is less pronounced in the obese (as if there were less necessity for conserving their stores of fat) but amounts to a considerable saving in energy output in the starving person who begins at a normal weight.[25, 33] The converse, that excessive eating might increase the basal metabolic rate, does not appear to be an important factor in the regulation of weight.[34] The basal metabolic rate in obese persons is characterized by approximately the same range of variability as in those of normal weight, the rates for the overwhelming majority falling within normal limits.[30] This normality is misleading, however, as shown by Strang and Evans.[33] The heart, liver and other viscera are providing for the production of 1,610 calories per 24 hours at basal conditions in our man of 150 pounds but when he gains to 300 pounds those same viscera are maintaining an organism which produces 2,170 calories, an increase of 34 per cent (table 1).

## Etiology

The concept of endogenous and exogenous obesity was championed early in the century by von Noorden,[35] and it has remained popular since. Newburgh [23] has expressed the feeling that the distinction is unimportant and that all obesity is exogenous since all fat is derived from the consumption of food in excess of requirements and because there have been no well controlled cases in which there was failure to lose weight on a sufficiently restricted diet. On the other hand it has been argued that all obesity is endogenous since the factors which initiate the overeating, such as psychologic conflicts or hypothalamic damage, originate within the person.[36] It would seem wisest to abandon the terms "endogenous" and "exogenous." [37]

The etiology of obesity will be discussed under a number of headings in this paper, but the outline should not be taken as a classification of obesity. Rather it should be considered as a list of mechanisms which have been proposed, of which only a few have been accepted as of any importance.

*Hypothalamic Damage.* Injury to the hypothalamus has been shown to interfere with a variety of self-regulatory functions such as temperature control and water balance. Injury to the paraventricular nuclei in the posterior portion of the hypothalamus causes obesity which results prin-

* Calculations were made by means of the Boothby-Berkson nomogram [31] and the factor for predicting weight loss given by Wilder.[26]

cipally from a great increase in appetite beginning abruptly after the damaging procedure.[29, 38] Hypothalamic changes rather than the originally presumed pituitary damage are now thought to have been responsible for the obesity observed by Fröhlich in his famous case reported in 1904.[39] Since pituitary damage alone seems to cause no pronounced constant change in weight,[29] and because the term "Fröhlich's syndrome" has been used frequently to describe the child or adolescent whose genitalia are partly obscured by masses of adipose tissue, it would seem desirable to abandon this term.[39]

Soon after the epidemic of encephalitis which occurred in 1918 a variety of symptoms began to appear in its victims.[40, 41] Among other manifestations of the postencephalitic syndrome there was obesity, and there is good evidence to believe that this was a result of damage to the hypothalamus which in turn increased the intake of food.

*Injury to the Cerebral Cortex.* The possibility that tumors of the frontal lobe may cause obesity has been discussed but the evidence is not convincing.[13]

*Psychologic Factors.* As the phylogenetic scale is ascended the cerebral cortex exerts an ever greater modifying influence on the functions of the lower nervous centers. As the individual matures, the cortex also assumes a greater control over such basic functions as eating, sleeping and procreation. There can be no argument but that our civilization has modified all such functions tremendously, and the aspect that each presents in various cultures is chiefly a mirror of that culture. Eating has acquired a considerable social significance in our own social order, not only in the nature and time of meals but in the amount eaten.[14, 42]

While it is true that most infants and children have less modification of their hypothalamic impulses by the cerebral cortex than do adults, yet Bruch [14, 43] has shown in a series of fundamental articles that obesity of psychologic origin can begin early in childhood. The mothers of such children would go to extremes in protecting their children from even the minor conflicts of living but paradoxically would entertain great ambitions for them. These children would be prevented from playing with other children and would be bathed and dressed by their mothers far beyond the usual age for such care. Within families containing obese children there is frequently a great emphasis on food. Desserts and candies are used as rewards for good behavior; conversation centers around delicacies of the table; and the child gains the feeling that food is the end and purpose of life. The mothers of obese children were found by Bruch [14] to be starved emotionally, disappointed in their husbands, worried over domestic strife and often disappointed in the sex of their children. As if in compensation these mothers attempt to pour out a love to their children that they do not honestly feel. In such an attempt they give the most obvious things, food, protection from the unpleasantness of work and contact with other children "who might play rough"; still these mothers are unable to give their children true affection. Similar situations undoubtedly occur in the lives of the lean, however.

Such a situation acting upon a child can lead to obesity in a number of ways. The protection from rough play and exertion diminishes the amount of energy expended. The atmosphere of gormandizing and the continual urging to eat will increase the amount of food eaten. Furthermore, the emotional starvation of the child who perceives the real emptiness of his mother's show of affection may lead to a compensatory increase in food consumption as though the child were trying to satisfy his emotional hunger by the eating of food.

While these factors have been repeatedly demonstrated by several observers, it may properly be asked whether similar factors do not frequently occur without the development of obesity. This view finds some confirmation in the investigations in the etiology of anorexia nervosa.[44] Here is a syndrome, almost invariably a manifestation of an emotional conflict, which has many close similarities to obesity while superficially completely different. Both are disorders of the mechanism which regulates the quantity of food intake. Frequently anorexia nervosa is preceded by obesity or the two conditions may alternate.[44] Both are more frequent in women than in men and both respond most dramatically to proper diet and psychotherapy. This response to diet and psychologic treatment alone is dramatic when contrasted with the numerous articles urging the use of endocrine substances and giving support to endocrinologic theories of causation of the two conditions.

The emotional factors which led to obesity initially should not cause the physician to overlook the conflicts which result from obesity and tend to perpetuate it. The obesity itself becomes a handicap which prevents the patient from obtaining exercise. This in turn diminishes energy output and causes further weight gain. The obesity is sometimes unconsciously used by the patient as a means of protection against doing unpleasant things. Obesity may repel suitors and protect the obese girl from the responsibilities of marriage. It may play a part in the selection of an occupation, preventing the obese person from doing difficult work.[17] The feeling of being set apart from other people because of the physical disfigurement of obesity tends to cause a certain amount of emotional starvation which perpetuates the increased appetite. Not only must the physician overcome the factors which initiated the weight gain but he must solve those which have arisen as a result of the obesity.

*Endocrine Factors.* One of the most regrettable practices in medicine is the attempt to diagnose numerous endocrinologic aberrations by means of slight variations in distribution of body fat.[45, 46] These elaborate classifications into types have little or no basis in controlled investigation and are usually misleading.[27, 47]

Pituitary body. No definite pituitary obesity has been proved. Cushing's disease now seems to be associated more closely with the adrenal cortex. The posterior lobe of the pituitary has been implicated because some have expressed the belief that an excess of the antidiuretic hormone may cause obesity by retention of water.[48] We are acquainted with no experimental

studies which have produced obesity in animals or human beings by the injection of pituitrin, a simple proof if this theory had any basis in fact. Recent experiments have suggested that the pituitary gland may regulate fat deposition through the lactogenic hormone.[49] This awaits confirmation.

Thyroid gland. In myxedema and hypothyroidism without myxedema, there is no increased incidence of obesity.[50, 51]

Adrenal glands. Hyperfunction of the adrenal cortex may result in Cushing's syndrome. In this condition there is frequently an increase in the total amount and always a characteristic distribution of the adipose tissue. Restriction of diet in Cushing's syndrome will cause loss of weight as in any other obese person.[12, 23]

Pancreas. True hyperinsulinism (that due to a functioning islet cell tumor) appears to cause obesity by means of an increased appetite which depends upon pronounced hypoglycemia.[52] It has been shown in animals that increased appetite results during insulin therapy only if the hypoglycemia approaches shock levels.[53] Obesity is mentioned as a symptom of the functional hypoglycemia described by Rennie and Howard,[54] but not of that reported by Alexander and Portis.[55] In well-developed obesity, hyperglycemia rather than hypoglycemia is considered characteristic.[23] Therefore it seems probable that hypoglycemia plays an unimportant part in the production of obesity.

Gonads. There is no definite proof that the gonads have significant effect upon the amount of fat in man,[27, 47] although they may influence its distribution. This contrasts with the effect in animals in which castration is frequently used as a means of increasing the deposition of fat.

Pineal body. The evidence is inconclusive that the pineal body has any influence on fat deposition.[56]

*Genetic Factors.* The Laurence-Moon-Biedl syndrome consists of mental deficiency, retinitis pigmentosa, hypogenitalism, obesity and polydactyly and appears to be inherited in a recessive manner.[57] The Morgagni-Stewart-Morel syndrome is perhaps better called "hyperostosis frontalis interna" and is inherited in a dominant manner.[58] It is manifested almost invariably by internal hyperostosis of the frontal bone and headache; frequently by obesity, impotence, amenorrhea, benign hypertensive cardiovascular disease, hirsutism, psychosis of indefinite nature or psychoneurosis, fatigability and weakness; and sometimes by disturbances in olfaction, Bell's palsy, diplopia and amblyopia. Headache is so constant that this diagnosis should be considered in all patients complaining of cephalalgia.[58] In neither of these disorders is there good evidence of endocrine dysfunction or of a disturbed fat metabolism which might cause obesity.

Gurney [59] found that obesity is much more frequent in some families than in others. Experiments with the yellow mouse have demonstrated a form of obesity which is inherited in a Mendelian manner.[60] However, it remains to be demonstrated whether the gene or environment is the more important factor in human obesity. While at present we cannot state definitely the

importance of heredity in obesity, we can emphasize to the patient with fat parents that he will respond to treatment in exactly the same way as will a person with parents of normal weight. Such a patient should be told that fat is just as dangerous to him as to anyone else and that the fact that his parents were fat cannot be used as an excuse to avoid the necessary corrective measures.

*Constitutional Abnormality of the Adipose Tissue.* An abnormal avidity of the adipose tissue of the person "predestined" to be obese has been postulated and named "lipophilia."[61] No proof of this exists.[12, 62] An entity known as "progressive lipodystrophy" characterized by wasting above the waist and obesity below is poorly understood[63] and the emaciation appears to be the significant pathologic aspect of this condition.

Dercum's disease, or adiposis dolorosa, is a syndrome consisting of tender and painful fat nodules in a patient partly disabled by weakness and psychoneurotic symptoms.[63] It has not been established as an entity and nothing of certainty is known of any cause or pathologic physiology.

*Disorders in the Use of Energy.* Excessive gastrointestinal absorption. This has been disproved in experiments which show that obese and normal persons absorb the same proportion of calories, nitrogen and fat from their diet.[23, 62]

Static obesity. Obesity due to inactivity and a diminished output of energy means that the appetite mechanism has failed to adjust the appetite to the energy requirements.[15]

Increased efficiency of the obese in doing work. Actually the obese person has a decreased mechanical efficiency and expends extra energy in doing the same amount of work.[32, 64]

Abnormal respiratory quotients. The respiratory quotient and its vagaries have been intensely studied for clues to the cause of obesity but no significant deviations have been found.[30]

Reduced specific dynamic action. This abnormality has not been demonstrated in obesity when the specific dynamic action is calculated properly.[65]

Negative phase of metabolism. Bernhardt[66] thought he had discovered a lowering of the metabolic rate to less than the basal rate after exercise or eating which was peculiar to the obese and effected an economy of energy which explained the development of obesity. This hypothesis was disproved by Wilder.[64]

Luxuskonsumption. This was a device postulated by Grafe and Graham[67] to explain why the normal person did not get fat. The normal person was thought to undergo an acceleration of metabolism after eating which consumed excess food. An absence of this phenomenon was suggested as an explanation for obesity. This theory was disproved by Wiley and Newburgh.[34]

Ketosis. Ketosis in fasting obese patients has been studied for clues to the origin of obesity, but no consistent abnormalities have been found.[68]

*Water Retention.* Water retention has been suggested as a primary

cause of obesity.[45, 48] In the absence of pitting edema it is doubtful whether any large accumulation of weight could take place from water retention alone.

## Treatment

There are no absolute contraindications to reduction of weight. A number of conditions in which reduction had best be done slowly and perhaps only when the patient is grossly obese are active or recently active tuberculosis, active peptic ulcer, gout, cirrhosis, Addison's disease and chronic ulcerative colitis. All of these conditions, except gout and peptic ulcer, tend to cause loss of weight so that the incidence of obesity in patients who have such diseases is low. It should be remembered that a properly devised reduction diet is often more nearly ideal for the therapy of the patient's condition than is the diet which is unrestricted in calories and which is selected by the patient himself after a few general directions given by the doctor.

One should be particularly certain that all essential foods are present in diets of children and pregnant women. Old age, hypertension and coronary artery disease are certainly no bars to reduction but rather are urgent reasons for it.

*Diet.* This is the most important measure in weight reduction. There is fairly good agreement that a reduction diet should contain an adequate supply of protein (1 gm. or more for each kilogram of body weight), a minimum of fat and enough carbohydrate to prevent wasting of protein. Such a diet permits the loss of large quantities of adipose tissue with little or no wasting of the protein structures of the body. Multiple vitamin supplements are advisable. It is advisable to add sufficient skimmed milk to the diet so that the patient does not require added calcium which, in the forms ordinarily prescribed, are poorly absorbed. The caloric content of the diet should be low enough to insure a definite weight loss and high enough to permit the inclusion of essential food materials. Such diets will provide a range between 600 and 1,500 calories and the selection of the diet should depend upon the physician's estimate of the situation. Space prevents publication of diet lists in this article, but representative diets may be found in the following references [12, 25, 26] and in a monograph by Rynearson and Gastineau now in press.

It is encouraging to the patient to be told that he will lose a definite amount each week. This can be calculated in the following manner:

1. Determine the caloric requirement for 24 hours at basal conditions by means of the Boothby-Berkson nomogram,[31] which is available in Wilder's primer for diabetics. Use the patient's actual height and assume a weight 30 pounds less than his actual weight in employing the nomogram.
2. Add 50 per cent.
3. Subtract the caloric value of the reduction diet selected.
4. Multiply by 0.002. The result obtained is the weight in pounds which will be lost in one week.[26]

Psychotherapy. Under this term can be placed the impression the personality and attitudes of the physician make upon the patient. Under this term can also be included all of those nebulous psychologic factors that make up the doctor-patient relationship. The physician who by his manner inspires confidence and a desire to follow his orders is most likely to succeed.

Ross[69] has shown quite well how the physician completely convinced of the efficacy of a certain treatment will by his manner transmit that conviction to the patient. If there is a large psychologic element in the illness concerned, then a remarkable improvement follows and the physician is further impressed by the worth of his therapy. A similar phenomenon may occur in the treatment of obesity. The doctor who believes he has found an endocrine or other type of preparation that will cure obesity will have the patient return to his office at frequent intervals for injections. The patient, impressed by the doctor's enthusiasm for his drug, becomes hopeful for success and anxious to aid in every way possible. Under such circumstances it is not surprising that the diet instructions are followed more closely and a good result is obtained. Thus the physician is further convinced of the efficacy of his drug. It is only when the doubting physician uses the drug that it fails.

A disadvantage to the use of any medication is that the patient may decide that the medication is the important factor in therapy and that a few violations of the diet will be of no consequence. Therefore we feel that it is best in most instances to tell the patient that his fat comes from eating too much and that reduction of the amount of food is the only way to reduce his excess weight. Most patients appreciate the honesty of this approach and will coöperate.

Superficial psychotherapy in the form of encouragement and reassurance may be sufficient in the majority of cases, but often the internist will find himself listening to the story of a profound neurosis and occasionally may be forced to refer such a patient to a trained psychiatrist.

*Drugs.* Thyroid speeds the metabolism, causes a negative nitrogen balance,[70] exerts a direct toxic action on the heart [71] and has long been used for the treatment of obesity. It is probable that small doses (1 to 2 grains [0.065 to 0.13 gm.] daily) of thyroid are inactivated [72]; larger doses may cause undesirable loss of body protein and an increased strain on a cardiovascular system already overburdened with an obesity-accelerated metabolism.[25, 33]

For these reasons it seems unreasonable to urge the use of thyroid, although many physicians find its use to be without harm when the patient is followed carefully and occasional determinations of the basal metabolic rate are made.

Other endocrine preparations have been used without effect in obesity. A few of these have been posterior and anterior pituitary extracts, ovarian extracts and estrogens.

Amphetamine and other sympathomimetic amines [15] have been used as

metabolic stimulants and as depressors of the appetite mechanism. It is probable that sufficiently large doses will cause a true depression of the appetite,[73, 74] but it is also likely that an elevation in basal metabolic rate and blood pressure lasting for several hours will follow.[75] Because this effect probably will not be detected if the basal metabolic rate is determined in the morning 12 or 15 hours after the last administration of the drug, many authors report that amphetamine has no effect on basal metabolic rate.

These amines share with all other medications the fault that they divert the patient's attention from the diet, the most important factor.[16] The use of amphetamine in obesity, within such limits as may be necessary to produce a reduction of appetite of the individual, has been approved by the Council on Pharmacy and Chemistry of the American Medical Association.[76]

In all fairness it should be added that many physicians are more enthusiastic regarding the use of these drugs than are we and they may be correct. More controlled observations are necessary before conclusions are reached.

Dinitrophenol is ineffective without diet limitation and its toxic reactions have caused its use to be stopped.[77]

Belladonna has been used [35, 78] but the results are not conclusive.

Diuretics may give the physician and patient a false sense of achievement by causing the excretion of a few pounds of water.[48]

*Salt Restriction and Heat Treatments Which Encourage Perspiration.* These are effective in much the same manner as diuretics. They are of no real value, all weight loss by their agency representing only water.

*Exercise and Massage.* These have no effect on local deposits of fat.[79, 80] Exercise is a relatively ineffective means of using energy and vigorous exercise is not wise in most obese patients.[23]

*Surgical Measures.* Procedures by which large amounts of fat have been removed have not proved practical.

## Summary

Obesity is one of the most pressing and dangerous health problems we face today. Much can be accomplished to improve the health of the general population by a vigorous effort to encourage the obese to reduce.

The development of obesity seems most frequently to depend upon a derangement of the appetite control mechanism. Circumstantial evidence suggests that this mechanism may reside within the hypothalamus and that its functions may be considerably modified by the cerebral cortex. Obesity may result from the inheritance of an appetite control center which demands more food for satiation. On the other hand, the important factor of environment cannot be ignored. Cerebral cortical function in the form of neuroses may modify the more automatic appetite control mechanisms.

A few unusual forms of obesity are recognized. The postencephalitic form results from injury to the hypothalamus. The Laurence-Moon-Biedl and the Morgagni-Stewart-Morel syndromes are rare conditions depending upon heredity.

Many other causes of obesity have been suggested but no good evidence exists for other than those already listed.

No abnormal metabolism has been demonstrated in obesity.

Therapy depends upon the limitation of caloric intake. Endocrine products and diuretics are neither necessary nor desirable parts of the reduction program.

Physicians are not unanimous in approving the use of thyroid extracts or stimulating drugs such as amphetamine. Most physicians do agree that the patient's attention should not be diverted from the diet as the fundamental basis for treatment.

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# THE POVERTY OF THE IMMUNOLOGICAL MECHANISM IN PATIENTS WITH HODGKIN'S DISEASE *

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Hodgkin's disease manifests itself as a proliferation of reticuloendothelial tissues, for which as yet no cause or causes have been established. Numerous kinds of bacteria have been found associated with this disease. Of these, many have in turn been proclaimed as the etiological agent only to be later unmasked as coincidental invaders. An interesting parallel to this fact is the increased susceptibility of these patients to intercurrent infections of various sorts; again here many different kinds of bacteria have been isolated. This greater susceptibility to infection seems paradoxical in the face of the massive proliferation of reticuloendothelial tissues, the cells of which, we have good reason to believe, are responsible for the production of antibodies.

In the light of this information it appeared desirable to examine the immunological mechanism of patients with Hodgkin's disease in the hope of elucidating some aspects of the pathogenesis (if not the etiology) of the disease. Accordingly a study was made of the case records of a large number of patients with Hodgkin's disease, with special reference to their immunological responses.

## Material

The material was obtained from several institutions in Memphis and Nashville in Tennessee, from Duke Hospital in Durham, North Carolina and from Charity Hospital in New Orleans. In Memphis the case records were studied at the John Gaston, the Baptist, the Methodist, and the Saint Joseph's Hospitals; while in Nashville the records were examined at the Vanderbilt and Nashville General Hospitals and at the Hubbard Hospital of the Meharry Medical College. In some of these institutions not all case records were available for study since the diagnosis file in the record room was of relatively recent introduction. Only those cases were studied in which the diagnosis was proved by biopsy or autopsy. Moreover, since the serological test for syphilis is a common procedure and, indeed, the immunological test most frequently used, the study was limited to those patients on whom such a test was done. Actually only a small number of patients were omitted because of this final restriction.

The names of patients of one institution were checked against those of the others in order not to include a patient more than once in the series. A few patients had visited more than one institution.

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TABLE I

The Distribution of Age, Sex, and Color of Patients with Hodgkin's Disease According to Hospital Sources

| | White Males | | | | | | | | White Females | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age in Years | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 |
| John Gaston | 0 | 3 | 5 | 2 | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 |
| Baptist | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| St. Joseph's | 2 | 0 | 2 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Methodist | 0 | 0 | 0 | 2 | 1 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nashville General | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Vanderbilt | 1 | 5 | 8 | 13 | 9 | 3 | 2 | 0 | 0 | 2 | 7 | 6 | 4 | 3 | 4 | 0 |
| Duke | 0 | 7 | 15 | 15 | 9 | 7 | 2 | 1 | 1 | 4 | 3 | 4 | 2 | 2 | 2 | 0 |
| Charity | 1 | 1 | 2 | 7 | 2 | 2 | 3 | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 1 |
| Total White | 4 | 16 | 32 | 40 | 25 | 18 | 8 | 1 | 2 | 8 | 12 | 11 | 9 | 6 | 8 | 1 |

| | Colored Males | | | | | | | | Colored Females | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age in Years | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 |
| John Gaston | 1 | 2 | 2 | 0 | 3 | 4 | 1 | 1 | 0 | 3 | 0 | 1 | 0 | 1 | 0 | 0 |
| Meharry | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vanderbilt | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Duke | 5 | 0 | 3 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 |
| Charity | 0 | 3 | 3 | 4 | 3 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| Total Colored | 6 | 5 | 9 | 8 | 8 | 6 | 3 | 1 | 0 | 3 | 4 | 6 | 0 | 2 | 0 | 0 |
| Total Both Races | 10 | 21 | 41 | 48 | 33 | 24 | 11 | 2 | 2 | 11 | 16 | 17 | 9 | 8 | 8 | 1 |

The following data were recorded in each case: name, age, sex, color and the results of all immunological studies made upon the patient. In all, the case records of 262 patients were examined.

## Results

*Age, Sex, and Color Incidence.* The distribution of cases according to age, sex, and color is shown in table 1 and figure 1.

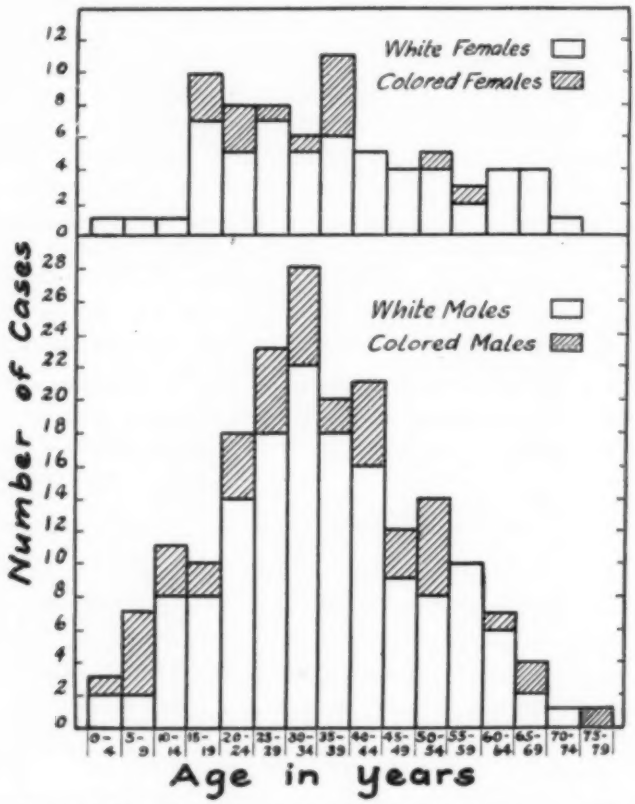


Fig. 1. Cases of Hodgkin's disease grouped according to sex, color and age (five year periods).

The age given is the one at which the diagnosis was first definitely established by an examination of the tissues; in the great majority of cases this was done by biopsy. In only a small number of cases (20) was the diagnosis first made at autopsy. Included in this series of patients were 144 white males, 57 white females, 46 colored males and 15 colored females. The ratio of males to females was 2.53 among the white patients, 3.07 among the colored patients, and 2.64 for both races.

An examination of figure 1 shows that very few cases occurred before the age of puberty. After puberty there was a sharp rise in the incidence

of the disease in both sexes, the bulk of the cases occurring in the reproductive period. Of a total of 72 female patients, three cases (4.2 per cent) were 14 years of age or less, 48 (66.7 per cent) between 15 and 44 years and 21 (29.2 per cent) over 44 years of age. Among the 190 male patients, 21 cases (11.1 per cent) were 14 years of age or less, 120 (63.2 per cent) between 15 and 44 years, and 49 (25.8 per cent) over 44 years of age.

*Syphilis.* Of the 61 colored patients, 10 (16.4 per cent) showed a positive serological test for syphilis. There were seven patients 10 years of age or less, of whom one had a positive Wassermann. The other 54 were 13 years of age or more, and of these nine (16.7 per cent) showed a positive reaction. This incidence is only about one-half that of the expected frequency (30 per cent) for colored adult patients.[1, 2, 3, 4]

Among the 201 white patients a positive serological reaction was present in seven (3.5 per cent). Fifteen patients were under 13 years of age and all of these showed negative tests; the seven positive cases occurred in the group of 186 adults. This incidence (3.8 per cent) approaches the expected frequency for white patients.

*Tuberculin.* The tuberculin skin test was done on 38 patients including 10 children and 28 adults. It was positive in only one patient who showed a 1 plus reaction to a dilution of 1/100. This is far lower than the expected frequency of about 50 per cent positive reactors.[5, 6]

There were three cases of associated active tuberculosis, but no tuberculin tests had been done on these patients.

*Typhoid.* Agglutination tests for the typhoid bacillus were done in 41 cases and for paratyphoid A and B in 32 cases—all with negative results.

TABLE II

Response of a Patient with Hodgkin's Disease to Inoculations of Typhoid Vaccine

| Date | Sept. 20 | Sept. 24 | Sept. 30 (10 days) | Oct. 4 (14 days) | Oct. 12 (22 days) | Oct. 28 (38 days) |
|---|---|---|---|---|---|---|
| "H" Agglutinins | 1:40 | | 1:40 | 1:80 | 1:80 | 1:80 |
| "O" Agglutinins | 1:20 | | 1:20 | 1:40 | 1:20 | 1:20 |
| Inoculations of Vaccine | 0.5 c.c. | 0.75 c.c. | 1 c.c. | | | |

In addition a study was made of the ability of a patient with Hodgkin's disease to respond to typhoid vaccine.* This patient (H. L.) was a 53 year old colored male who showed a 1 plus reaction to a 1/100 dilution of tuberculin and whose blood Kahn on admission was 1 plus; the latter reaction became negative three months later. He was given three intramuscular injections of typhoid-paratyphoid † vaccine over a period of 10 days; the volumes consisted respectively of .5 c.c., .75 c.c. and 1 c.c. Blood samples were taken before the course of vaccination and at 10, 14, 22 and 38 days respectively after the first inoculation. The results are shown in table 2. Before

* The agglutination studies were done by Dr. I. D. Michelson of the Division of Pathology and Bacteriology, University of Tennessee College of Medicine.

† Parke-Davis Typhoid-Paratyphoid Vaccine containing 2000 million bacteria per c.c.

the course the level of the "H" agglutinins was 1:40 and that of the "O" agglutinins 1:20. After vaccination the "H" agglutinins reached a maximum of 1:80 and the "O" agglutinins 1:40. Obviously this patient was unable to respond to the typhoid antigen. At that time he was in good condition. Moreover, the value of his total blood proteins was 5.2 grams per cent which, though slightly reduced, is not low enough to explain his deficient antibody response on the basis of hypoproteinemia.[7, 8, 9, 10]

*Brucella.* The immunological tests for Brucella were uniformly negative in the group of patients from Memphis, Vanderbilt Hospital and Charity Hospital in contrast to the findings at Duke Hospital where some of the patients showed positive responses. But even in the latter group, in which there was a high incidence of brucellosis, the immunological reactions were deficient.

Among the group of patients from Memphis agglutination tests were done in 12 and were all negative. Negative results were also obtained from the skin test in two patients and the opsonin test in one. This group includes one patient from whose lymph node Brucella was cultured; his agglutination, skin and opsonin tests all showed negative results.

In the series from Vanderbilt the agglutination test was done in 27 patients and was negative in all. The skin and opsonin tests were also negative, the former in eight and the latter in two.

In the group from Charity Hospital the agglutination for Brucella is listed as positive in one of 13 cases.

At Duke Hospital the agglutination reactions were studied in 31 cases. Of these, four showed a positive agglutination above a dilution of 1:640; Brucella was cultured from these four patients. The skin test was done in nine cases and was positive in only one. The opsonin test was positive in six of 19 cases. The complement-fixation test which was done in 13 cases was negative in 10 and positive in three.

Wise and Poston [11] reported the immunological studies made upon seven of the Duke patients with Hodgkin's disease from whom Brucella was cultured. In spite of the coexistence of the Brucella infection the immunological responses were poor. The skin test was done on four of these patients and was negative in all. The complement-fixation test was positive in three and negative in three. In four patients the agglutinins and opsonins were present in significant concentration early in the course of the Brucella infection, but later disappeared in spite of the persistence of the bacteremia. In one patient Brucella was found intermittently over a period of 10 months, but all this time there were no demonstrable agglutinins; at the end of this period the patient finally developed a titer of 1:2,560. Another patient showed no immune responses in spite of the presence of Brucella during life. One patient gave negative agglutinin and opsonin tests; cultures during life were negative, but Brucella was found at autopsy. In a later paper on the coexistence of Hodgkin's disease and infection with Brucella, Forbus and

associates [12] summarized the experience at Duke University by saying that practically none of their patients showed specific antibody reactions in what they regarded as significant titer.

*Tularemia.* Agglutination tests were made in 41 cases; in 40 the result was negative and in one case it was positive in a 1:80 dilution. The skin test was done in one case and was negative.

*Proteus X–19.* The agglutination test was run on 20 patients, all with negative results.

*Miscellaneous.* Finally, the following miscellaneous immunological tests were negative: heterophile agglutinins in four cases, complement-fixation test for malaria in one, cold agglutinins in two, trichinella skin test in one, histoplasmin skin test in two, echinococcus skin test in two, agglutination test for Flexner bacillus in five, Frei test in one, and the complement-fixation test for amebiasis in one.

## Discussion of Results

*Reaction to Tuberculin.* In the present series of patients, tuberculin tests were done on 38, with only one positive reaction. This incidence of 2.6 per cent is much below that of the expected frequency (about 50 per cent) for the general population.

Aronson [5] in 1931 made a study of the incidence of positive tuberculin reactions in the South. For Gibson and Lake Counties in Tennessee the incidence among white persons under 20 years of age ran about 54 per cent and 45 per cent respectively and for colored patients of the same age group 63 per cent and 56 per cent respectively. For persons over 20 years old the incidence was about 55 per cent for the white group and 80 per cent for the colored.

A current study by Dr. I. D. Michelson [6] of this Department of the incidence of tuberculin reactions among the patients of the John Gaston Hospital has shown a frequency of 52 per cent positive reactors among the general hospital population.

The tuberculin reaction in patients with Hodgkin's disease has been studied extensively. There is a good review of the subject in Wallhauser's article.[13]

Parker [14] states that "practically all authors are agreed that by far the great majority of cases of Hodgkin's disease give a negative reaction; even in cases with an associated active tuberculosis."

Steiner [15] found negative skin reactions to both avian and human tuberculin proteins in Hodgkin's disease.

Morquio [16] found the tuberculin test negative in patients with Hodgkin's disease even in those with associated tuberculosis. He believed that Hodgkin's disease causes a condition of anergy of the patient, by which the reaction to tuberculin is rendered negative, even when tuberculosis is present.

Bastai [17] reported 24 cases of Hodgkin's disease in which the tuberculin

reaction was studied. In 22 patients the reaction was negative and in only two was it slightly positive. This anergy he found to be absolute, even up to a dilution of 1 : 30. Moreover, this anergy occurred in both the early and late stages of the disease. Exceptionally, the tuberculin-allergy reappeared in patients who had roentgen-therapy and were in the stage of remission.

Marval [18] reported seeing patients with tuberculous lymphadenitis and intense tuberculin-allergy develop Hodgkin's disease (proved anatomically) with accompanying anergy to tuberculin. Moreover, he attempted active immunization with BCG in patients with Hodgkin's disease; as controls he had a group allergic to tuberculin and another normal non-allergic group. The last two groups became tuberculin positive, but the patients with Hodgkin's disease still remained tuberculin negative. He has found that patients with Hodgkin's disease can stand daily subcutaneous doses of as much as 2 c.c. of crude tuberculin without reaction. His patients with Hodgkin's disease were also anergic to avian tuberculin. He explains this tuberculin anergy by saying that since Hodgkin's disease is primarily a disease of the reticulo-endothelial system, patients with this disease would be inhibited in their reaction to tuberculin.

Evidently patients with Hodgkin's disease are anergic to tuberculin, even in the presence of active tuberculosis. This low incidence of reaction to tuberculin in patients with Hodgkin's disease cannot be explained by any protection against tuberculosis which Hodgkin's disease may confer, for if anything tuberculosis is more common among patients with this disease than among the general population.

*Syphilis.* There were 61 colored patients with Hodgkin's disease. Seven of these were 10 years of age or younger and one had congenital syphilis with a positive Wassermann reaction. The remaining 54 colored patients were 13 years of age or older; nine of these showed a positive serological test for syphilis. The incidence of a positive reaction among the colored adults was 16.7 per cent, which is about one-half the expected frequency of 30 per cent.

Of the 201 white patients there were 15 children all with negative serological reactions. The other 186 white patients were 13 years of age or more; of these seven showed a positive test. This gives an incidence of 3.8 per cent positive reactors for the white adult group. This approaches the incidence of syphilis among the white population in general.

The following data indicate the expected frequency of positive reactors among the white and colored populations. The recent survey of the population between the ages of 14 to 50 years in Jefferson County, Alabama [1] (which includes the city of Birmingham) showed that the incidence of syphilis among the colored group was 30.86 per cent and among the white 3.07 per cent. A study of syphilis among the draftees [2] (males between 21 to 35 years of age) gave the following incidence in Tennessee, North Carolina, and Louisiana:

| | | | |
|---|---|---|---|
| Tennessee | | Urban—white | 5.84 per cent |
| | | colored | 31.32 per cent |
| | | Rural—white | 2.96 per cent |
| | | colored | 22.89 per cent |
| | Urban and Rural Combined | white | 3.94 per cent |
| | | colored | 27.78 per cent |
| North Carolina | | Urban—white | 3.42 per cent |
| | | colored | 32.36 per cent |
| | | Rural—white | 2.61 per cent |
| | | colored | 19.40 per cent |
| | Urban and Rural Combined | white | 2.85 per cent |
| | | colored | 23.74 per cent |
| Louisiana | | Urban—white | 4.53 per cent |
| | | colored | 31.79 per cent |
| | | Rural—white | 3.16 per cent |
| | | colored | 24.29 per cent |
| | Urban and Rural Combined | white | 3.79 per cent |
| | | colored | 27.20 per cent |

In 1940 the incidence of syphilis among the patients at Duke Hospital [3] was as follows: 29 per cent for the colored males, 32 per cent for the colored females, 2.7 per cent for the white males and 3.2 per cent for the white females.

At the Charity Hospital [4] a positive serological reaction was found in 26 per cent of the colored and in 6 per cent of the white patients.

The average incidence of syphilis among the colored patients at the John Gaston Hospital for the years 1940 to 1943 inclusive was 28 per cent. Since the group of cases of Hodgkin's disease occurred over many years the following additional control was set up for the colored group at the John Gaston Hospital: for each colored patient with Hodgkin's disease, a case record was picked at random to correspond to the same year, age, sex, and color. This was done twice; among the first control group about 40 per cent showed a positive Wassermann reaction and among the second about 32 per cent.

It is clear from these data that the expected frequency of a positive serological test among the colored adult population is about 30 per cent. Of our 54 adult colored cases of Hodgkin's disease 46 were accounted for by Duke Hospital, Charity Hospital, and the John Gaston Hospital. The incidence of positive reactions among the adult colored patients with Hodgkin's disease was 16.7 per cent, considerably lower than the expected frequency of 30 per cent. A statistical analysis, using the Chi-square method,[19] showed this difference to be significant.

Of the white adult patients with Hodgkin's disease 3.8 per cent had a positive serological test for syphilis. This approaches the expected fre-

quency among the white population in general. It should be pointed out, however, that since syphilis is 10 times more common among the colored than among the white population, more significance can be attached to our findings in the smaller group of colored patients with Hodgkin's disease than to our data derived from the white group.

Wallhauser [13] collected 268 cases of Hodgkin's disease from the literature in which the incidence of syphilis was studied. If to these are added the 60 cases of Krueger and Meyer,[20] nine positive reactors are found among 328 patients, or 2.7 per cent. These original articles do not state how many of the patients were colored. Certainly some colored patients were among the group, for in Simmons and Benet's article [21] there appear the photographs of two colored patients.

The significantly low incidence of positive serological reactions for syphilis in the group of colored patients with Hodgkin's disease requires explanation. It would seem unlikely that they are somehow protected against syphilis. It might be argued that this group was less exposed to syphilis owing to a generalized weakness and a loss of libido. This appears highly improbable, however, for it would require a considerable loss of strength to nullify so potent a stimulus among a group of colored adults. Probably, the explanation is similar to that for the anergy to tuberculin, namely, that patients with Hodgkin's disease are poor producers of antibodies. Syphilis probably occurs in a group of patients with Hodgkin's disease with the same frequency as among the general population, but owing to the poverty of their antibody production the incidence of a positive Wassermann reaction would be less among them than among the control group. For example, one of our colored patients (H. L.) on admission showed a 1 plus reaction to 1 mg. of tuberculin and a 1 plus Kahn reaction. Although he did not receive antisyphilitic treatment, one month later the Kahn reaction was negative. He died two months after the last examination and at autopsy a typical syphilitic aortitis was found.

*Typhoid.* Agglutination reactions for typhoid were done in 41 patients and for paratyphoid A and B in 32; all the results were negative. This, of course, is too limited an experience to be of any significance. I believe it significant, however, that one of the patients (H. L.) upon being given a a course of typhoid vaccination was unable to produce antibodies. He was in good condition at the time, and the total protein of his blood was 5.2 grams per cent. This again points to an underlying inability to produce antibodies.

*Brucella.* At Duke University a rather high incidence of infection with Brucella was found coexistent with Hodgkin's disease. For example, in a series of 24 cases of Hodgkin's disease studied during life 14 yielded Brucella by cultures of either blood or lymph node. In spite of this, practically none of these patients developed specific antibody reactions against Brucella in what was regarded as significant titer.[12] This is further evidence of the deficiency of the antibody-production mechanism in Hodgkin's disease.

*Other Immunological Reactions.* As for the other immunological reactions observed in this series the data are insufficient to warrant any conclusions.

Davidsohn [22] reported that in patients with Hodgkin's disease some of the normal antibodies, namely the iso-agglutinins and the agglutinins for sheep red cells, were present in about the same titer as in normal persons.

## Significance of Data

*Etiology and Pathogenesis.* It seems clear that patients with Hodgkin's disease are poor producers of antibodies. The anergy of these patients to tuberculin is well known, but the concept of anergy (failure of reactivity) should be enlarged to include a poor response to *all* types of antigens. The poverty of their antibody production mechanism is manifest not only in their inability to make the antibodies which are fixed to cells (such as in tuberculin hypersensitivity) but also the circulating antibodies of the types found in syphilis, brucellosis, and typhoid fever.

In view of the importance of the level of the blood proteins [7, 8, 9, 10] in the manufacture of antibodies it becomes necessary to study this factor in Hodgkin's disease. Starlinger and Winands [23] found that in Hodgkin's disease the blood shows a normal total protein, an absolute and relative increase in fibrinogen, a moderate absolute and relative increase in globulin and a significant absolute and relative decrease in albumin. In the terminal cachexia the protein content progressively decreases and the globulin returns to a normal value, with the relative increase preserved.

The plasma proteins were studied in eight patients at the John Gaston Hospital. The results, which are shown in table 3, are in accord with the findings of Starlinger and Winands.

Table III

Values in Grams Per Cent of Plasma Proteins in Eight Cases of Hodgkin's Disease at the John Gaston Hospital

| Patient | Total Proteins | Albumin | Globulin | Fibrinogen |
|---|---|---|---|---|
| C. R. S. | 5.3 | | | |
| W. M. | 4.6 (with edema) | | | |
| W. L. | 7.5 | | | |
| G. S. | 5.5 | 3.2 | 1.1 | 1.2 |
| H. L. | 5.2 | 3.4 | 1.8 | |
| E. C. | 8.6 | 2.8 | 3.5 | 2.3 |
| C. H. | 6.2 | 2.8 | 2.6 | 0.8 |
| H. J. | 7.3 | 3.5 | 2.8 | 1.0 |

While the above data are limited, in that the various globulin fractions were not studied, it seems justifiable to say that the poor antibody response in Hodgkin's disease is not due to hypoproteinemia.

Since it has been suggested that antibody production might occur on the basis of proteolysis and proteosynthesis by the macrophage system,[24] the process of phagocytosis in Hodgkin's disease should be examined.

McJunkin [25] injected neutral red into a lymph node which showed typical Hodgkin's tissue. He found that the supravital reaction to neutral red of the large cells of Hodgkin's tissue was like that of the reticuloendothelium of normal and hypertrophied lymph nodes.

Mankin [26] in tissue culture studies of Hodgkin's tissue noted the development of two types of reticular cells. One was a variegated type of cell similar to that which developed in cultures of normal lymph nodes; this cell was phagocytic. The second type of cell, not found in cultures of normal nodes, was a "homogeneous" cell incapable of phagocytosis. As the cultures matured, the first type of cell lost its capacity of phagocytosis and appeared to go over to the second type; the latter increased in numbers and became the predominant reticular cell.

M. R. Lewis [27] noted that in tissue cultures of Hodgkin's tissue the Dorothy Reed cells were non-phagocytic.

This problem was studied recently in the case of H. L., the same patient who failed to respond to typhoid vaccine. This patient had an enlarged epitrochlear node, about 3 cm. in diameter. About 3 c.c. of a 1 per cent aqueous solution of trypan blue was injected intracutaneously and subcutaneously into the area drained by this node. Twenty-four hours later this node was removed. At the operation it was seen that all the tissues around the node were stained blue. Coursing over the capsule of the node were several small lymphatics which were stained a deep blue. The node itself, however, was unstained. Most of the tissue was fixed for microscopic study while the remainder was used for tissue culture. On microscopic examination no dye was found in the cells. This failure to take up the dye is not conclusive evidence of failure of phagocytosis since the afferent lymphatics might have been blocked by the proliferating Hodgkin's tissue.

Tissue cultures were made of some of the tissue removed at operation. At 24 and 48 hours there was a vigorous growth of macrophages and reticular cells. To these in vitro cultures trypan blue was added and after 24 hours' incubation the cultures were examined. There was no evidence of phagocytosis of the dye by the growing cells. Again it might be argued that this experiment is inconclusive in that the dye might not have penetrated the fine plasma coagulum in which the cells were growing. These studies will be pursued.

The data on phagocytosis in Hodgkin's disease are inadequate. More work must be done along these lines before any evaluation can be made of the rôle of this factor as a possible explanation for the anergy in this disease.

The next question that arises is whether this "total anergy" in Hodgkin's disease is a purely secondary phenomenon or whether it is a primary disturbance. The proponents of the former hypothesis may argue that in Hodgkin's disease the reticuloendothelial system becomes replaced by the Hodgkin's tissue so that its capacity to produce antibodies is interfered with. This explanation has been suggested by Morquio,[16] Marval [18] and Wall-

hauser.[18] The latter, in discussing the relationship between tuberculosis and Hodgkin's disease, states: "Probably a majority of students of the disease have considered *B. tuberculosis* as a secondary invader. If it is true, as many believe, that the lymphoid and reticulo-endothelial systems are concerned in the defense against tuberculosis it is hardly surprising that a lighting up of a tuberculous focus should occur when these systems have been practically eliminated or seriously injured by a disease such as lymphogranuloma."

Lillie [28] has suggested that the more frequent presence of organisms in Hodgkin's nodes may be accounted for by the lack of antibody-production by neoplastic reticuloendothelial tissue.

On the other hand, let us consider the hypothesis that in Hodgkin's disease the anergy is a primary phenomenon. The fundamental disturbance in Hodgkin's disease may be a primary metabolic dysfunction resulting in a deficiency of the enzyme system or systems necessary for proteolysis and proteosynthesis which occurs in antibody production. On the basis of this deficiency, one of many antigenic stimuli may set up a proliferation of reticuloendothelial tissues in an attempt to increase the cells which ordinarily make antibodies. This reticuloendothelial hyperplasia would normally result in increased antibody production; but in Hodgkin's disease there is merely a futile proliferation of functionless tissue. The cells are there, but their enzyme systems are deficient. According to this hypothesis, one would not expect to find a single etiological agent. In connection with this, one is reminded that the body has a limited number of ways of responding to injury, as illustrated by the multiplicity of stimuli which set off the response known as "inflammation."

A survey of the literature shows that only a few writers have been bold enough to suggest such an explanation. Brandt [29] believed that Hodgkin's disease is merely a manifestation of a severe damage to the reticuloendothelial system produced by various causes and not a disease of one kind alone. Desjardins,[30] impressed by the high frequency of diverse infections among patients with Hodgkin's disease, has suggested that chronic infections may start the disease.

Probably most students of the disease would prefer to accept the more orthodox explanation that the poor immunological mechanism in Hodgkin's disease is purely a secondary phenomenon resulting from the serious damage to the reticuloendothelial system. A characteristic response to the unorthodox suggestion that Hodgkin's disease may be caused by more than one etiological agent is that of Krumbhaar's [31] reaction to Desjardins' opinion. Krumbhaar wrote: "Desjardins' view that any chronic infection may start Hodgkin's as well as other lymphomatoid diseases in those hereditarily predisposed seems such a bad case of 'post hoc propter hoc' that it will probably obstruct progress but little." In spite of this criticism it seems to me that Desjardins' view merits consideration. At this point, both views should be considered

as equally probable; for certainly the evidence does not favor one over the other. An entrenched opinion that Hodgkin's disease must be caused by a single etiological agent may obstruct progress as much as any other opinionated viewpoint.

In any case, the poor immunological mechanism in Hodgkin's disease stands as a fact, regardless of whether it is a primary or a secondary event. Moreover, it serves to elucidate some of the factors associated with the disease. It probably explains the higher frequency of intercurrent infections and the increased susceptibility of these patients to infections. Also, it accounts for the finding of different kinds of bacteria in patients with this disease. It explains why, at various times, the tubercle bacillus,[32, 33, 34, 35] the diphtheroid bacillus,[36, 37, 38] Brucella [11, 12, 39, 40] and other bacteria have been isolated from the tissues of patients suffering from Hodgkin's disease. It should recommend caution to any investigator who, on finding a certain organism frequently associated with Hodgkin's disease, makes claims to it as the etiological agent.

*Treatment.* The finding of a deficient immunological mechanism in Hodgkin's disease would suggest that treatment, in addition to roentgen-therapy, should be directed along lines to stimulate antibody-production in order to increase resistance to infection. The diet should include a high proportion of proteins and other factors which have been shown to enhance antibody-production.

Recently pyridoxin [41, 42, 43] has been found to be essential for the manufacture of antibodies and the maintenance of lymphoid tissues. This substance was recently given to a patient (H. L.) shortly after the diagnosis was made. At that time the patient's general condition was rather good. In addition to roentgen-therapy, he was given 150 mg. of pyridoxin daily over a period of two months until his death. One was struck by the rapid worsening of his status, which went on to death in a matter of two months. Examination of the tissues at autopsy revealed a marked change in the histological picture of the Hodgkin's tissue. The picture had changed from the pleomorphic "granulomatous" appearance to that of a malignant neoplastic process, not unlike a reticulum cell sarcoma. Of course, it is not possible at this time to evaluate the rôle of pyridoxin in the acceleration of the hyperplasia which occurred in this case. In a few authenticated cases, Hodgkin's disease has progressed from a "granulomatous" to a "sarcomatous" phase. In view of the rôle of pyridoxin in the maintenance of lymphoid tissue, one wonders whether this substance was responsible for the increase in growth of the Hodgkin's tissue in this patient. The use of pyridoxin in the treatment of Hodgkin's disease should be studied further. Moreover, since pyridoxin maintains lymphoid tissue and may have accelerated the growth of the Hodgkin's tissue in this patient, a trial should be made of desoxypyridoxin,[44] a powerful inhibitor of pyridoxin. Indeed, Stoerk [43] has already speculated that desoxypyridoxin may be of use in the treatment of tumors of the lymphoid tissue.

## Summary

Patients with Hodgkin's disease are deficient in their ability to produce antibodies. This deficiency is generalized and is illustrated by their anergy to tuberculin, by the lower incidence of positive serological tests for syphilis, by their inability to make antibodies against Brucella when brucellosis coexists, and, in the case of one patient, by his inability to respond to typhoid vaccine.

This deficiency of the immunological mechanism cannot be explained on hypoproteinemia, since the total protein values are normal in these patients.

The rôle of the possible failure of phagocytosis has been discussed but there are insufficient data to draw any conclusions.

Consideration has been given as to whether this immunological deficiency is a secondary phenomenon subsequent to the damage of the reticuloendothelial system by a single etiological agent, or whether in Hodgkin's disease the primary disturbance is a metabolic one resulting in a deficiency of antibody production so that many different kinds of stimuli may cause a hyperplasia of Hodgkin's tissue as a compensatory, albeit futile, phenomenon.

In either case, this poverty of the immunological response of these patients explains their increased susceptibility to infection. Moreover, it explains why at various times different kinds of bacteria have been isolated from their tissues and proclaimed as the etiological agent.

It has been suggested that in the treatment of patients with Hodgkin's disease an attempt should be made to improve their ability to make antibodies in order to increase their resistance to infection. The use of high protein diet and pyridoxin in this regard has been discussed.



### Acknowledgment

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# CLINICALLY PRIMARY TUBERCULOUS PERICARDITIS *

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TUBERCULOSIS of the pericardium is a more common finding for the pathologist than for the clinician. It more often occurs in the presence of demonstrable active tuberculous lesions elsewhere in the body, notably the lungs. Less frequently it occurs as a "primary" tuberculosis of the pericardium, or as a "clinically primary" tuberculosis of the pericardium. It is in the latter two that the etiological agent is frequently unsuspected. The tubercle bacillus is notoriously difficult to demonstrate in serous fluids or exudates, requiring exhaustive search over months in many instances. No one hesitates to make a diagnosis of tuberculosis of the pleura or peritoneum when other causes of pleurisy or peritonitis can be reasonably excluded.[1] Just as "clinically primary idiopathic pleurisy with effusion" is considered tuberculous in nature, unless proved otherwise, so should "clinically primary idiopathic pericarditis with effusion" be suspected as being tuberculous in nature. The "clinically primary" type of tuberculous pericarditis is that in which, at the onset of symptoms, there are no clinically demonstrable active tuberculous lesions elsewhere in the body,[2] although at some later date active foci may become demonstrable in other organs. This does not preclude the presence of hidden active foci at the onset. In distinction, primary tuberculosis of the pericardium, as defined by Thompson,[3] was that in which, as far as one could ascertain at autopsy, the pericardial involvement was either the only or the oldest tuberculous lesion. Rokitansky [4] is credited with being the first to comment on primary tuberculous pericarditis. He believed that it was dependent upon an earlier tuberculous lesion. Similarly, Harvey and Whitehill,[1] Blalock and Levy,[5] and Bellet, McMillan and Gouley [6] are of the same opinion. Hedbloom [7] apparently believes that primary tuberculous pericarditis does occur without the presence of any other previous tuberculous lesions. Recently, Terplan [8] has shown that a primary tuberculous focus can and does exist in the pulmonary parenchyma, with no involvement of the regional or mediastinal lymph nodes or lymphatic system. By inference drawn from this study, it may be possible for a primary tuberculous focus to exist in the pericardium.

The incidence of tuberculous pericarditis, in general, is not high. In an examination of 7,219 protocols, Norris [9] reported 1,780 tuberculous subjects, in which tuberculous pericarditis was present in 82, an incidence of 1.1 per cent. Likewise, Osler [10] in 1,000 autopsies reported 275 tuberculous subjects, of which seven had tuberculous pericarditis.

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In 1921, Hedbloom[7] collected 13 cases of primary tuberculous pericarditis. Rawls[11] added one case, and Thompson[3] in 1933, in a review of the literature, collected 21 cases of primary tuberculosis of the pericardium, to which he added seven more. Most of his cases were in the adhesive stage; apparently, only in one was the tubercle bacillus suspected ante mortem, the remaining being diagnosed correctly after autopsy examination.

Riesman,[2] in 1901, called attention to the "clinically primary" type of tuberculous pericarditis. Following this, other cases[12, 13, 14, 15, 11, 16, 17] of tuberculous pericarditis, falling within this category, appeared in the literature up to 1929, at which time Clark[18] in a careful search of the literature, found and reviewed 11 cases, and added two more of his own. Bellet, McMillan and Gouley,[6] in 1934, reported 17 cases of tuberculous pericarditis, of which they believed six to be clinically primary. Case histories were given in only two of the six. Platou,[19] Fine and Katz,[20] and Mackay[21] each reported a case of the clinically primary type. In Thompson's[3] series of seven cases we believe three to be of the clinically primary type, similarly six of Harvey and Whitehill's[1] cases belong in this classification. Babcock,[22] Burch and Winsor,[23] and Mitchell[24] each reported a case of tuberculous pericarditis, all of which appear to fall within this category. In Keefer's[25] 20 cases of tuberculosis of the pericardium, eight are apparently clinically primary. In a report of 42 cases, Blalock and Levy[5] stated that approximately seven were "primary from the clinical viewpoint." Cushing[26] and Cushing and Moritz[27] reported an interesting case which they believed to be a pericardial diverticulum and tuberculous pericardial effusion; however, at post mortem the lesion proved to be a tuberculous abscess of the anterior chest wall which communicated with the pericardial cavity. No other tuberculous lesions were found elsewhere in the body.

A total of 50 cases which we believe to be "clinically primary" tuberculous pericarditis have been collected from the literature, to which we add three of our own. This paper concerns itself with a discussion of several interesting findings in our cases and also an analysis of the symptoms and signs of the cases reviewed.

## Case Reports

*Case 1.* C. O., a white male, aged 60, was admitted June 6, 1941, with the complaint of headache and fever of two weeks' duration. Two weeks prior to admittance he was in an automobile accident, at which time he was temporarily unconscious and fever up to 103° F. appeared. Several days prior to entry a slight productive cough developed. There was no history of tuberculosis.

Physical examination revealed a well developed and nourished male who appeared acutely ill, with a fever of 103.4° F., pulse rate of 90, respiratory rate of 24, and blood pressure 100 mm. Hg systolic and 65 mm. diastolic. Lungs were clear. Cardiac dullness appeared within normal limits, with normal rhythm and no murmurs. Abdomen was negative.

Urinalysis showed trace of albumin, an occasional hyaline cast, and red and white cells. Hemoglobin was 13.5 grams. Leukocyte count was 8,050 with normal dis-

tribution. Tuberculin skin test was positive to 1:100 dilution of old tuberculin. Roentgenograms of chest revealed a cardiac silhouette of water-bottle type, indicating pericardial effusion; and minimal left pleural effusion. The only pulmonary pathologic lesion was a calcified Ghon primary lesion in the left base. Electrocardiogram revealed changes consistent with pericardial involvement.

Course: A pericardiocentesis performed 10 days after entry yielded 150 c.c. of cloudy yellow fluid, which was positive for tubercle bacilli on guinea pig necropsy six weeks later. About two weeks after entry a palpable but non-tender liver was noted. Auricular fibrillation appeared also at this time for which the patient was digitalized. Improvement followed for the next five months, during which time the size of the cardiac shadow decreased slightly. A year after entry a roentgenogram revealed the presence of a right pleural effusion and the cardiac shadow still enlarged. Right thoracentesis was performed and 850 c.c. of amber colored fluid were removed, which was negative for tubercle bacilli on guinea pig inoculation. In July 1942 the patient became suddenly very dyspneic. The liver was tender and extended several fingers'-breadth below the right costal margin, but no ascites nor peripheral edema was demonstrable. A pericardiocentesis was performed and 600 c.c. of fluid were removed, with relief to the patient. At this time pneumopericardium was instituted. Several days later dyspnea recurred, associated with a fever of 102° F. A right thoracentesis was performed, with removal of 2,000 c.c. of fluid, which was negative for tubercle bacilli on guinea pig inoculation. Between July and November of 1942 the patient received six pericardiocenteses, the largest amount of fluid withdrawn being 1,200 c.c. Pneumopericardium was maintained following each tap. Over the subsequent 11 months two courses of tuberculin therapy were given with seemingly beneficial results.* Several attempts at removal of pericardial fluid were made during June 1943, but no fluid was obtained. Fluoroscopy and roentgenograms showed the cardiac shadow decreasing in size. Improvement continued except for occasional episodes of dyspnea and right upper quadrant pain. The patient was discharged in September 1943, asymptomatic and ambulatory, the heart appearing normal in size. No pulmonary lesion had been demonstrable, as yet.

Patient was readmitted January 20, 1944, complaining of fainting; however, he left the hospital the next day, prior to workup and against medical advice.

Patient was admitted for the third time on March 16, 1944, with a fever of 102° F., pulse rate 120, respirations 24, complaining of fatigue, shortness of breath and a mild productive cough. Examination revealed râles and wheezes in both lung bases. The area of cardiac dullness was normal, heart tones were distant, and gallop rhythm was present. Sputum was negative for acid-fast bacilli on smear. He improved on symptomatic treatment and was discharged on April 11, 1945.

Patient was admitted for the fourth time on January 31, 1946, because of orthopnea and indigestion. Temperature was 98.6° F., pulse 88 and respirations 22. The lungs were clear. The heart was not enlarged, the tones distant, rhythm regular and no murmurs were audible. The abdomen revealed ascites and a paracentesis was performed, with removal of 1,000 c.c. of dark green fluid. Ascitic fluid, gastric contents and urine were all negative on smear and guinea pig inoculation. The patient improved and was discharged on March 29, 1946.

The patient's final entry was on April 24, 1946, complaining of dyspnea. Examination revealed ascites, for which a paracentesis was done and 400 c.c. of clear amber colored fluid were removed, which proved negative for tubercle bacilli on smear. The cephalin cholesterol flocculation test was 3 plus. Serum proteins were 6.54 gm./100 c.c. Blood urea nitrogen was 23 mg./100 c.c. and the non-protein nitrogen 37 mg./100 c.c. The patient's course was progressively downward and he died on June 13, 1946.

* Results to be discussed in another paper at a later date.

Necropsy findings: Adhesive and fibrotic pericardio-mediastinitis; portal cirrhosis and ascites; young miliary tubercles of the myocardium, liver and lungs.

*Case 2.* L. A., a white male, 42 years of age, was admitted on November 13, 1944, complaining of shortness of breath, weakness and cough of one and one-half months' duration. The patient was well until one and one-half months ago when he developed a slightly productive cough, associated with weakness and shortness of breath. He was examined physically and fluoroscopically several times by his doctor, and the only positive finding was "enlarged heart." There had been a loss of 20 pounds in weight over this period of time. The past history was non-contributory, except for the fact that both his parents had been ill with "pneumonia" for the past several months. Physical examination revealed a thin man, appearing chronically ill, with a temperature of 100.4° F., pulse 85, respirations 22, blood pressure 110 mm. Hg systolic and 70 mm. diastolic. The chest was thin. The resonance, breath sounds, and vocal fremitus at the right lung base were decreased. The outline of the heart was not determinable upon percussion, nor was the point of maximum intensity palpable. A high pitched systolic murmur was heard to the left of the sternum in the fourth interspace. The abdomen was protuberant, and no organs were palpable.

Hemoglobin was 12.5 gm., leukocyte count was 6000 with 84 per cent neutrophiles and 16 per cent lymphocytes. There were occasional red and white blood cells in the urine. Several 24-hour sputum specimens were negative for acid-fast bacilli on smear. Tuberculin skin test was negative to 1.0 mg. old tuberculin. The electrocardiogram showed sinus tachycardia and low QRST in all leads. Roentgenograms of the chest revealed no evidence of active pulmonary disease, but the heart was markedly enlarged to both sides.

Course: The patient ran an intermittent type of fever, between 99° and 102° F. About 10 days after entry he became quite dyspneic, the neck veins were distended, and a friction rub near the apex became audible. Pericardiocentesis was performed, with removal of 150 c.c. of straw-colored fluid, which proved to be positive for the tubercle bacillus on smear. The patient's distress was slightly relieved following this. Bilateral pleural effusion appeared one month after entry, requiring removal of fluid for relief. A total of three left and 12 right thoracenteses and seven pericardiocenteses were done. Pneumopericardium and pneumothoraces were maintained until death on March 28, 1945.

Necropsy findings: A markedly thickened pericardium, multiple bilateral pericardio-diaphragmatic adhesions; miliary tubercles in lungs, pleurae, liver, spleen, kidneys, and peritoneum.

*Case 3.* P. C., a Negro male, 30 years of age, was admitted on March 30, 1945, complaining of shortness of breath of four days' duration. About three weeks before entry the patient developed a dry cough, with chills and fever. Four days previously he began to experience difficulty in breathing associated with a choking sensation. The physical examination revealed a well developed and nourished Negro in obvious respiratory distress. The temperature was 103.6° F., pulse 84, respirations 24 and blood pressure 120 mm. Hg systolic and 90 mm. diastolic. The tonsils were enlarged and the mucous membranes injected. No lymphadenopathy was present. Lungs were clear. The area of cardiac dullness was enlarged to the left and right, and heart tones were faint, rhythm regular and no murmurs were heard, but a friction rub was present to the left of the sternum in the fourth interspace. The liver was tender and palpable several fingers'-breadth below the right costal margin. The remaining examination was negative.

Hemoglobin was 11.7 gm. and red blood cell count was 4.1 millions. A leukocyte count was 7,000 with 90 per cent neutrophiles and 10 per cent lymphocytes. All sputum examinations were negative, and the tuberculin skin test was positive to

1:10,000 old tuberculin. The electrocardiogram showed low amplitude in Leads I and II, with inverted T-waves in all leads and sinus tachycardia. Fluoroscopy and roentgenograms revealed a waterbottle shaped heart and clear lung fields.

Course: Two days after entry a pericardial tap was done, with removal of 400 c.c. of bloody fluid. The patient felt greatly relieved. The pericardial fluid was negative for acid-fast bacilli on both smear and guinea pig inoculation. Barium meal showed antero-posterior compression of the esophagus, due to the effusion, with delayed filling of the stomach. Smear of stomach contents obtained by gastric lavage performed a month after entry revealed occasional acid-fast bacilli. The patient was fairly comfortable until about three months later, when he became dyspneic again, and was found to have left pleural effusion. Thoracentesis was performed, and the fluid was proved positive for tuberculosis by means of guinea pig inoculation. Subsequently, right pleural effusion and ascites developed, and also evidence of cardiac failure, requiring digitalization. His fever ranged from 99° to 103° F., and he was dyspneic continually during the remainder of his course. Seven months after entry he began to expectorate foul smelling sputum in large quantities. Fluoroscopy showed an infiltration in the left lung, with a small apical cavity. He died on October 6, 1945.

Necropsy findings: Adherent and thickened pericardium; multiple cavitations in the left lung; tuberculous enteritis and ascites.

## Discussion

One of the cases cited (case 1) shows that these patients may tolerate a relatively large pericardial effusion over a considerable time. This can be explained on the basis that the accumulation of fluid in the pericardial cavity is sufficiently slow to allow the pericardium to accommodate itself to the increased distention, thereby allowing the intra-pericardial pressure to remain below the level which causes serious embarrassment to the circulation.[7] This patient tolerated a pericardial effusion for approximately 24 months. The last pericardiocentesis to yield fluid was performed 16 months after the initial one. Several unsuccessful attempts to remove fluid from the pericardial cavity were performed 24 months after the onset of the effusion.

Pneumopericardium is helpful in both diagnosis and treatment. Upon production of a pneumopericardium, the findings of a normal sized heart, a thickened pericardium, and the absence of murmurs point strongly to tuberculosis as the causative factor. In treatment it offers the possibility of limiting the tuberculous exudate to the pericardial cavity, thereby averting a later adhesive pericarditis.[7, 28] Others [23] doubt its value and believe that it may increase fibrosis. Ackermann [29] believes it to be beneficial.

In case 2, the interesting findings were a tuberculin skin test negative to 1.0 mg. of old tuberculin, and the rapid accumulation of fluid, necessitating frequent removal from both pericardial and pleural cavities for relief. Apparently, the process was so acute and fulminating that sensitivity to tuberculin had not developed, thus substantiating the fact that a positive tuberculin skin test is not absolutely essential to denote the presence of a tuberculous condition in the body.

In case 3, although acid-fast bacilli were not found in the pericardial fluid,

the clinical picture was sufficiently adequate for the diagnosis of tuberculous pericarditis to be made. Finding tubercle bacilli later in the gastric contents proved the nature of the etiological agent, during which time the pericardial involvement was still the prominent feature of the case.

*Analysis of Cases:* We have attempted to analyze the prominent clinical findings of clinically primary tuberculous pericarditis; however, sufficient data are available in only 37 of the cases in this study. These findings are shown in table 1.

Age: The ages ranged from 9 to 80 years, of which 15 (41 per cent) were within the first three decades and the remaining 22 cases (59 per cent) after the third decade of life.

Sex: Twenty-nine (79 per cent) cases were males.

Race: In only 29 of the 37 cases was the race stated. Sixteen (43 per cent) were colored, the remaining 13 (35 per cent) being white. This dis-

TABLE I

Prevailing Findings in 37 Cases of Clinically Primary Tuberculous Pericarditis

| | | |
|---|---|---|
| (1) *Age* | | |
| 0–15 years old | | 5 (14%) |
| 16–30 | | 10 (27%) |
| 31–45 | | 7 (18%) |
| 46–60 | | 11 (30%) |
| 61 and over | | 4 (11%) |
| (2) *Sex* | | |
| Male | | 29 (79%) |
| Female | | 8 (21%) |
| (3) *Race* | | |
| Colored | | 16 (43%) |
| White | | 13 (35%) |
| Unknown | | 8 (22%) |
| (4) *Presenting Symptoms* | | |
| (*a*) Fever | | 33 (89%) |
| 99–100° F. | 5 (15%) | |
| 101–103° F. | 16 (48%) | |
| above 103° F. | 12 (37%) | |
| (*b*) Shortness of breath | | 28 (76%) |
| (*c*) Edema | | 25 (68%) |
| (*d*) Cough | | 19 (51%) |
| (*e*) Weakness | | 16 (43%) |
| (*f*) Chest pain | | 13 (35%) |
| (*g*) Headache | | 4 (11%) |
| (*h*) Abdominal pain | | 4 (11%) |
| (5) *Prominent Physical Findings* | | |
| (*a*) Distended neck veins | | 12 (37%) |
| (*b*) Pericardial friction rub | | 8 (21%) |
| (*c*) Arrhythmias | | 10 (27%) |
| (*d*) Pericardial effusion | | 24 (65%) |
| (*e*) Pleural effusion | | 21 (57%) |
| Bilateral | 12 (57%) | |
| Left only | 6 (29%) | |
| Right only | 3 (14%) | |
| (*f*) Ascites | | 15 (41%) |
| (*g*) Palpable liver | | 9 (24%) |
| (6) *Laboratory Findings* | | |
| (*a*) Leukocyte count | | |
| Normal | | 15 (41%) |
| Leukocytosis | | 6 (16%) |
| Leukopenia | | 4 (11%) |
| Not reported | | 12 (37%) |
| (*b*) Tuberculin skin test | | |
| Positive | | 16 (43%) |
| Negative | | 1 (3%) |
| Not reported | | 20 (54%) |
| (*c*) Diagnosis based on: | | |
| Guinea pig inoculation | | 13 (35%) |
| Smear | | 6 (16%) |
| Culture | | 1 (3%) |
| Autopsy | | 17 (46%) |
| (7) *Duration of Illness* | | |
| 0–6 months | | 23 (63%) |
| 7–12 months | | 8 (21%) |
| 13–24 months | | 3 (8%) |
| over 2 years | | 3 (8%) |
| (8) *Outcome* | | |
| Died | | 31 (84%) |
| Improved or "recovered" | | 6 (16%) |

tribution is of interest because the incidence of tuberculous pericarditis in general, as described in the literature, is much higher than the above figures for the negro race.

Symptoms and Signs: Fever and shortness of breath occurred with the greatest frequency, the former being present in 33 (89 per cent) of the cases, the latter in 28 (76 per cent). Of the 33 with fever, 5 (15 per cent) were below 100° F.; 16 (48 per cent) from 101 to 103°, and 12 (37 per cent) over 103° F. A high fluctuating temperature prevailed, but no typical curve was found. Dependent edema was common, occurring in 25 (68 per cent) of the cases. Cough and weakness were present in about half the cases. Chest pain occurred in one third of the cases, its location being variable, and was not severe. Headache and abdominal pain were not common, each happening in only four (11 per cent) cases. Distention of the neck veins, indicating increased intra-pericardial pressure, was present in 12 (37 per cent) cases. (Experimental work indicates that approximately 100 c.c. of pericardial fluid will initiate a rise in venous pressure.[30]) Pericardial effusion was present in 24 (65 per cent) cases and pericardial friction rub in only eight (21 per cent). Friction rubs occurred in those cases with effusion as well as those without. In most cases the pericardial fluid was sero-sanguineous in nature. The amount of fluid removed at a single tapping varied from 50 to 2,500 c.c. The effusions recurred frequently, necessitating repeated pericardiocenteses for relief of symptoms in many of the cases. In almost all cases in which they were performed, both roentgenography following pneumopericardium and postmortem examination revealed the presence of a normal sized heart and the absence of valvular disease. Distant heart tones and an absent apical impulse were common findings. Cardiac arrhythmias occurred in 10 (27 per cent) cases, auricular fibrillation being present in five, paradoxical pulse in four, and partial heart block in one. Sinus tachycardia was common in most cases. The electrocardiogram consistently revealed low voltage and changes in the S–T segment and T-waves. Pleural effusion occurred in 21 (57 per cent), 12 being bilateral; effusion was twice as common on the left as on the right, when unilateral. The presence of ascites was shown in 15 (41 per cent) and an enlarged palpable liver in only nine (24 per cent) cases. The leukocyte count was reported in 25, a mild leukocytosis being present in six (24 per cent), a leukopenia in four (16 per cent), and in the remaining 15 (60 per cent) cases was within normal limits. This uncommon occurrence of leukocytosis has been noted by others.[1, 23] It is worthwhile to note the disproportion between the fever and leukocyte count, which may prove to be an important differential point. In only 17 of the 37 cases was the tuberculin test mentioned. All were positive with the exception of one (case 2 in our series). This case was negative to 1.0 mg. of old tuberculin. An uncommon finding was jaundice, present in two cases.[19, 21] A choking sensation occurred in one. Other symptoms that are common to tuberculosis in the body were night sweats and weight loss. Finding of the tubercle bacillus was difficult in most cases,

requiring repeated smears, cultures, and guinea pig inoculations from all available sources. Many cases required months to demonstrate the organism. In 17 (46 per cent) cases the diagnosis was definitely established only at post mortem.

The duration of the illness lasted six months or less in the majority of cases (23 or 63 per cent). Only six (16 per cent) lived over one year. The duration of case 1 in our series is apparently the longest reported in the literature, lasting for five years before terminating fatally owing to miliary tuberculosis.

Nearly all cases (31 or 84 per cent) had a fatal outcome. Only six (16 per cent) were reported improved; surgical intervention was employed in several cases.[7, 22] However, the final results in these improved cases are unknown. It is conjectured that these improved cases might have simulated case 1, in that the latter was discharged improved five times, only to terminate fatally as a result of his primary disease.

Many [1, 18] believe that the commonest cause of death in the younger patients with tuberculous pericarditis is miliary tuberculosis, and that in the older age group is myocardial failure.

## Summary and Conclusions

Fifty cases of clinically primary tuberculous pericarditis have been collected from a review of the literature, to which three cases of our own have been added. The findings in 37 cases with adequate data are analyzed.

Involvement of the pericardium as the first clinical manifestation of active tuberculosis is not rare. The diagnosis should be seriously considered when: (*a*) there are presenting symptoms of unexplained fever, shortness of breath, edema, cough, weakness and chest pain; (*b*) there is evidence of pericardial involvement, viz. friction rub, effusion and characteristic abnormalities in the roentgenogram; (*c*) these findings are present in a male over 30 years of age, and of the colored race.

Emphasis is placed on the necessity of frequent and persistent examination of all materials available in order to find the tubercle bacillus. Failure to demonstrate them does not necessarily rule out the clinical diagnosis, as shown by the fact that almost half of the cases analyzed required postmortem confirmation.

Prognosis is unfavorable, most cases terminating fatally within a year.

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# THE EFFICACY OF MAINTENANCE DOSES OF DIGITALIS IN PREVENTING THE RECURRENCE OF CONGESTIVE HEART FAILURE *

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## INTRODUCTION

SEVERAL investigators [1] have demonstrated that patients with heart disease associated with auricular fibrillation develop congestive heart failure when digitalis is withheld. Katz, Sokolow, Weinberg and Plaut [2] were the first investigators to study the effect of maintenance doses of *folia digitalis* on the circulation of patients with chronic congestive heart failure associated with regular sinus rhythm. They presented studies on four patients who showed a prompt increase in the venous pressure, circulation time, and weight when digitalis was withheld and who also developed clinical evidence of congestive heart failure. We had begun a similar study several months before the publication of this work.

## METHOD AND MATERIALS

One hundred and four patients with heart disease associated with regular sinus rhythm who had been discharged from Charity Hospital after treatment for congestive heart failure were followed in the clinic at intervals of from one to four weeks over a period of from six months to two years. At the time the study was begun most of the patients had been taking 0.1 to 0.3 gm. of *folia digitalis* for several weeks or months after discharge from the hospital. Measurements of venous pressure, circulation time, vital capacity and weight were made during a one to three month period at intervals of from one to four weeks; then digitalis was discontinued and the same measurements repeated at the same intervals of time. The degree of dyspnea, orthopnea and edema was recorded as well as the presence or absence of râles, the size of the liver, the cardiac findings and the subjective state of the patient. Patients were advised to avoid sudden exertion of any kind, limit the fluid and salt intake insofar as possible and report to the clinic whenever they developed a cough, other evidence of infection or increasing symptoms of congestive heart failure.

## RESULTS

Of the 104 patients 79 were colored and 25 were white. There were 60 males and 44 females with an age incidence of from 31 to 80. Sixty-one had

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hypertensive cardiovascular disease, 21 arteriosclerotic, 2 rheumatic and 20 syphilitic.

The data were broken down according to the variation in the measurements of the venous pressure, circulation time, vital capacity, weight, heart size and frequency of the development of congestive heart failure while the patients were being studied.

In general it can be stated that none of the criteria employed for measurement of the circulation revealed any significant differences during the time digitalis was given to the patient and during the period that the drug was withheld. In no instance did we find a patient showing a consistent increase in venous pressure, circulation time and weight when digitalis was withheld with a prompt reversal of these measurements when the drug was readministered.

TABLE I

The variations and averages of the measurements of the vital capacity, venous pressure, circulation time and weight are shown for nine patients with heart disease during the periods when they were taking maintenance doses of folia digitalis and during the time when the drug was being withheld. See text.

| Pt. | Vital Capacity in Liters | | Circulation Time in Seconds | | Venous Pressure in Cm. of Water | | Weight in Pounds | |
|---|---|---|---|---|---|---|---|---|
| | Without Digitalis | With Digitalis | Without Digitalis | With Digitalis | Without Digitalis | With Digitalis | Without Digitalis | With Digitalis |
| 3 | 2.50–2.12 (2.31) | 2.83–1.70 (2.12) | 35–30 (32) | 36–24 (27) | 22–12 (13.5) | 16–7.5 (8.6) | 154–142 (146) | 150–138 (142) |
| 21 | 1.42–2.12 (1.65) | 2.27–2.03 (2.12) | 28–25 (28) | 40–35 (35) | 30–12 (18) | 28–9.8 (17.9) | 133–118 (122) | 129–121 (124) |
| 26 | 3.82–3.31 (3.40) | 3.97–3.35 (3.54) | 37–27 (31.4) | 43–20 (31.4) | 17–8 (12.9) | 14–9 (10.4) | 141–135 (139) | 139–131 (133) |
| 35 | 2.60–2.12 (2.36) | 2.60–2.12 (2.41) | 30–19 (24.2) | 28–10 (20.8) | 16–11 (13.7) | 19–8 (13.2) | 176–165 (170) | 175–163 (170) |
| 36 | 2.17–1.65 (1.98) | 2.12–1.94 (2.03) | 17–13 (15) | 15–12 (13.7) | 15–8 (12.5) | 11.5–6.5 (8.2) | 133–123 (130) | 127–120 (123) |
| 45 | 1.94–1.42 (1.65) | 2.36–1.42 (1.84) | 18.5–11 (14) | 20–9.5 (13.6) | 20–17 (13.3) | 27–10 (10.7) | 231–228 (229) | 236–225 (229) |
| 50 | 2.74–1.56 (2.50) | 3.40–2.55 (2.93) | 35–14 (23.6) | 25–20 (23.2) | 21–6 (11.2) | 11–7.5 (9.4) | 159–146 (152) | 158–144 (151) |
| 57 | 2.64–146 (2.27) | 2.41–2.12 (2.30) | 43–35 (38) | 36–21 (30) | 21–7.5 (16.5) | 11–8 (10.5) | 212–200 (206) | 204–194 (199) |
| 63 | 2.31–1.23 (1.75) | 2.27–2.12 (2.23) | 16–12 (15.5) | 16–13 (14.7) | 17–12 (14) | 18–8.5 (14) | 187–160 (173) | 180–177 (178) |

Table 1 presents the variation and averages in the measurements of vital capacity, circulation time, venous pressure and weight for the 10 patients showing the most clear-cut differences in these measurements in the two periods of study. At least four and as high as 20 separate measurements

of the vital capacity, circulation time, venous pressure and weight were made during each period: First, when the patient was receiving maintenance doses of *folia digitalis* of from 0.1 to 0.3 gm. and, second, when the drug was withheld. It can be seen that there was a marked overlapping of the measurements in every instance and that the average differences between any of the measurements in the two periods are not statistically significant. Data for the remaining 90 patients are not given, since there was a random distribution both of the averages and ranges of the values in any given patient whether or not he was receiving maintenance doses of *folia digitalis*. Sixty-five of the 100 patients studied developed congestive heart failure requiring hospitalization while being studied, but the levels of the selected objective criteria of decompensation rarely indicated its approach.

We feel that our data substantiate the impression that these criteria are indicative of the presence of heart failure only when the process is well advanced. If repeated, or continuous, measurements of the venous pressure, circulation time and vital capacity could be made, it is very likely that fluctuations betraying the approach of congestive heart failure would be observed. Once congestive heart failure has been established, all or most of these measurements do indicate the presence and relative severity of the process. However, our data lead to the conclusion that if these measurements are made at intervals they are relatively crude methods for evaluating the approach of congestive heart failure. Our findings might indicate that the process (congestive heart failure) developed and became established during the time interval between the taking of the last measurements and the admission of the patient to the hospital. However, several of the patients studied were admitted to the hospital only two or three days after relatively normal readings had been obtained in the clinic, but at the time of admission were found to have sustained high venous pressures, prolonged circulation times and low vital capacities with physical findings of moderately advanced congestive heart failure. Whether or not repeated measurements made during the week prior to admission to the hospital might have revealed the onset and progression of congestive heart failure is a question which can be settled only by more extensive investigation. In the light of present evidence, an affirmative answer does not appear unlikely.

Several points of interest with reference to the circulatory measurements obtained were noted. As reported by Peabody [3] and confirmed by others,[4] patients with heart disease who are not in failure have, on the average, lower vital capacity and longer circulation time than do "normal" individuals of the same age group. This was confirmed in our study. The highest values in the "with digitalis" column were not necessarily obtained during the first week or two following the administration of digitalis and no consistent curve could be plotted for any individual measurement over the period of observation.

Changes in weight appeared just as sensitive as the level of the venous pressure, circulation time, or vital capacity in evaluating the presence or

approach of congestive heart failure. The vital capacity was more sensitive in a few patients who developed predominantly left heart failure. With the possible exception of changes in vital capacity and weight, detailed questioning of the patient with regard to dyspnea, orthopnea, and transient ankle edema, together with a careful physical examination, were more reliable in evaluating the state of the circulation than repeated measurements of the circulation time, venous pressure or heart size.

In 27 patients, measurements of the transverse diameter of the heart were made during the period of maintenance dosages and during the times when digitalis was withheld. Frank decompensation was not present when these teleoroentgenograms were made and no significant differences in the heart size could be detected in the group as a whole, as brief study of table 2 will

TABLE II

Comparative measurements of the transverse diameter of the heart, derived from six-foot teleoroentgenograms, are shown. Note the lack of significant differences in this measurement during the two periods of observation. See text.

| Pt. | Transverse Diameter of the Heart in Cm. | | Pt. | Transverse Diameter of the Heart in Cm. | |
|---|---|---|---|---|---|
| | Without Digitalis | With Digitalis | | Without Digitalis | With Digitalis |
| 1 | 15.2 | 15.2 | 15 | 16.2 | 21.1 |
| 2 | 14.4–13.9 | 17.4 | 17 | 16.8 | 16.3 |
| 4 | 14.7–14.9 | 14.1–14.3 | 20 | 14 | 13.3–13.5 |
| 5 | 14.5 | 14.9–13.9 | 22 | 13.6 | 14.9–13.4 |
| 6 | 13.5 | 13.0 | 23 | 17.8–17.7 | 18.5 |
| 7 | 18.1–17.2 | 18.2–16.8 | 26 | 19.5 | 19.6–19.4 |
| 8 | 15.3 | 15.7 | 27 | 18.3–16.3 | 17.0–15.7 |
| 9 | 14.0 | 13.2 | 29 | 13.7 | 13.2 |
| 10 | 15.5 | 15.0 | 30 | 12.5 | 14.5–14.1 |
| 11 | 16.1 | 17.1 | 31 | 15.1–14.3 | 14.8–14.1 |
| 12 | 16.0–15.2 | 15.4 | 32 | 16.1 | 15.4 |
| 13 | 15.1 | 16.4–15.5 | 33 | 16.2 | 15.7 |
| 14 | 22.1 | 19.9 | 34 | 15.3 | 13.9 |
| | | | 35 | 15.1 | 15.5 |

show. Stewart [5] demonstrated that the diastolic heart size decreases when the patient with congestive heart failure recovers and LaDue and Fahr [6] have shown that the decrease in diastolic heart volume is progressive during the period of compensation. It is also known that digitalis will diminish the diastolic heart size of the normal heart,[7] but it is not known how long this effect persists. Our data can only be interpreted as signifying that maintenance doses of *folia digitalis* given to patients who have had congestive heart failure fail to produce permanent and significant changes in diastolic heart volume once compensation is established.

The number of admissions to the hospital during the time when *folia digitalis* was withheld was 45, but was only 20 during the period in which patients were taking maintenance doses of digitalis. Because of uncontrollable factors, the differences in the number of hospital admissions while under study cannot be evaluated statistically but may have an intrinsic significance,

since more than twice as many patients developed congestive heart failure during the period without digitalis.

Patients taking maintenance doses of digitalis had fewer subjective complaints and said they were able to "do more" when they were receiving the drug, although evidence of this nature is highly unreliable because of the psychic and willful improvement that may have resulted from the fact that the patient was receiving medicine.

## Discussion

Our data suggest that the vital capacity, circulation time, venous pressure and weight are, at best, crude measurements of cardiac reserve and are less reliable in evaluating this important factor than a careful consideration of the symptoms and signs presented by a patient with heart disease. However, this in no way detracts from the value of these measurements in the study or evaluation of the degree of congestive failure present and of the mechanisms involved in the production and disappearance of cardiac decompensation.

The evidence presented here of the efficacy of maintenance doses of *folia digitalis* in preventing the recurrence of congestive heart failure, although not clear-cut, suggests that it may be desirable to keep patients who have had congestive heart failure on maintenance doses of *folia digitalis,* since the rate of recurrence is twice as great when the drug is withheld.

In another study [8] it was shown that once congestive heart failure is present the need for digitalis is increased. Six of the 20 patients who were readmitted to the hospital in congestive heart failure while taking 0.1 to 0.3 gm. of folia digitalis were given 0.8 to 1.6 mg. of lanatoside C intravenously with evident improvement. This suggests that frequent reëvaluation of the therapeutic level of digitalization is indicated. We discontinue digitalis for three weeks at six month intervals and then redigitalize the patients with regular sinus rhythm and place them on a maintenance dose of *folia digitalis* of from 0.1 to 0.3 gm. daily.

## Conclusions

1. Of the 104 cardiac patients studied, 45 were admitted to the hospital for recurrent congestive heart failure during a test period in which *folia digitalis* was withheld. However, there were only 20 admissions during a period in which these same 104 patients were taking maintenance doses of folia digitalis.

2. The transverse diameter of the heart is not appreciably affected by the taking of *folia digitalis* over a period of two to 24 months, in the fully compensated patient with heart disease associated with regular sinus rhythm.

3. Patients with heart disease have a definite diminution in the vital capacity and a prolongation of the circulation time even in the absence of congestive heart failure.

4. Measurements at frequent intervals of the vital capacity, circulation time, venous pressure and weight failed to demonstrate the efficacy of maintenance doses of *folia digitalis* significantly to improve the cardiac reserve of patients with heart disease associated with regular sinus rhythm.

5. Maintenance doses of from 0.1 to 0.3 gm. of folia digitalis should be given to patients with heart disease associated with regular sinus rhythm.

6. None of the criteria employed in this study gives any accurate appraisal of the proper maintenance dosage of *folia digitalis* for patients with heart disease associated with regular sinus rhythm.

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# THE MEDICAL HISTORY: A SUGGESTED TECHNIC FOR INTERNISTS AND GENERAL PRACTITIONERS *

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In the light of the experience of those who, like Dunbar,[1] believe that many of the errors in medical diagnosis and treatment can be traced to the medical history, a review of the status of the medically acceptable case record should provide material which could be used for determining some of the sources of error and how they might be avoided or minimized.

Medical histories have been recorded since the beginning of history itself. Devotees left their stories on the pillars of the temples before Hippocrates braved the dawn of modern medical science, and down the centuries have come the plaints of suffering and the observations of physicians as to what morbidities were responsible for the clinical aspects of disease. The turn of the last century was marked by an era sometimes referred to as the "Golden Age of Bacteriology." Microbial causes of disease began to replace outgrown theories of etiology, and with contemporary contributions in the fields of chemistry and physics, better understanding of morbid anatomy, increased specialization among physicians, and general improvement in medical diagnosis, medical progress has contributed to the addition of a decade in life expectancy in less than 50 years. The present day method of taking case histories came into common use in 1902, when Cabot [2] instituted the case record method of teaching, in contrast to the more arbitrary intuitive art of his time. His clinicopathological conferences were innovations, and for several years printed reports of these sessions were widely distributed by subscription among the medical profession. In 1906, Barach [3] described an observation chart to supplement the hospital records which then were commonly limited to a graphic chart with or without a separate page for doctors' orders. His chart provided a single line for the daily record of hospital occurrences, treatments, and results. He remarked, "As time goes on and medicine becomes more of a science and less of an art, the better for medicine, as empiricism is being replaced by a sound principle, we find that system is more and more essential and detailed records must be kept and preserved."

In more or less discriminating circles, the pattern of the modern medical history is relatively uniform. It includes, first, the patient's chief complaints: namely, the symptoms which bring the patient to seek medical care, how long they have existed and how they began. Next comes a supplemental organ system review with the idea of gaining more detailed information about the nature of the complaints and bringing to light any the patient

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has overlooked. Also included are statements concerning previous illnesses and the dates of their occurrence; then, the family history referable to the ages, health, and causes of death of near relatives, and finally, a social history which is limited to brief statements of the patient's age, intellectual level, birthplace, habits, and economic and social status. Whether or not this order is followed, the material represents what is usually required from the patient when he presents himself for examination at the hospital, clinic, or the office of his physician. It is not a history in the sense that it is a record of events according to their relationship or sequence, subject to review and analysis as documentary evidence, but is a collection of data, concerned primarily with what might be revealed by physical examination or laboratory means. As a corollary to such clinical findings, its importance as a diagnostic instrument varies according to the nature of the medical problem. It has been conservatively estimated that probably 50 per cent of the cases in general practice are specific short term disabilities requiring little more than the evaluation of objective symptoms for their identification. In such instances, a personal history might contribute little to the diagnosis of the condition for which the physician is consulted and be of only relative importance in matters of treatment. But at least 50 per cent of the general practitioner's patients, and a far greater proportion of the internist's, present multiple cumulative complaints, among which are the overlooked or forgotten past illnesses, undiscovered pathological processes of the present, and the so-called "functional" complaints, more critically designated "autonomic nervous system disturbances," where symptoms are often protean in character and where there may be functional abnormalities in blood pressure, basal metabolism, glucose tolerance, gastrointestinal functions, etc. Left to the interpretation of subjective symptoms listed in the usual case history on the basis of physical and laboratory examinations or the intuitive assumption of psychoneurotic content, one is sometimes faced with a dilemma from which escape may be found in over-emphasis of non-consequential findings. Should reference to a psychiatrist be made another history must be taken which has the effect of detaching the emotional factors from other elements in a diagnostic problem. Such situations, from which none are immune, provide adequate reason for us to contemplate the criticism directed to our methods of history taking.

Before considering in some detail the possible sources of error in diagnosis which might exist in the medical history it is suggested that three common faults may be found:

*First:* The time allocated to the patient's recital of complaints may be insufficient to allow clarification.

*Second:* Difficulty of integration of subject matter exists when symptoms are separately grouped by organ systems without reference to relationship or sequence.

*Third:* Limitation of the personal history to more or less abstract and

relatively unimportant items omits information essential to the identification of emotional causes of somatic complaints.

Errors attributable to the length of the interview may be found in the time-saving categorical question and answer technic, notably in regard to previous illnesses and chronic diseases. Categorical questions are frequently difficult to answer and often carry suggestions that will influence the replies. In prolonged illnesses, particulars relative to chief complaints and other symptoms may be influenced by the patient's previous medical experiences, conversations with family and friends, to say nothing about what they have learned from the newspapers, radio, and periodicals devoted to matters of physical and mental health. Their social, economic, and intellectual status color their statements, and emotional factors, notably elements of fear, anxiety, and hostility, which become part and parcel of every chronic illness, may disguise a simple syndrome of organic disease or constitute a syndrome of their own. Sometimes deliberate misstatements are made, and apparently for as many reasons as there are vagaries in human character.

The inclusion of information of past and present symptoms in the record of chief complaints and their subsequent grouping by organ systems without regard to relationship or sequence render their integration difficult in proportion to the number and variety of items to be considered. Accepting the validity of all assembled data, organization is often impossible and an intelligent review or summary frequently cannot be made.

An ever present source of error exists in the lack of material concerning the patient himself: how he acts when under stress; what physical symptoms he has when agitated or on trial; what handicap, physical or otherwise, he thinks he has for attainment in family, business, religious and social circles; what he thinks of himself as a person. This lack of material may more subtly interfere with the accuracy of interpretation by influencing the examiner to identify himself with the patient's emotional problems. It is easy to evaluate another person's difficulty in the light of one's own experiences, and too much attention can be focused upon immediate situations without an understanding of what personality factors and circumstances may have contributed to them. It may lead to supplementation of information given by the patient with or without his consent by interviews with members of his family or associates which may add to confusion unless they are for specific incidents or circumstances in the history that need verification. Unless the examiner is aware of these influences he may find himself in the position of being led rather than leading in his efforts to be of service. Years ago Cannon [4] described the physiological reactions to hunger, pain, fear and rage, but their importance in the syndrome of disease cannot be determined if no reference is made to them in the medical history.

With these facts in mind, it is obvious that our method of history taking has not kept pace with other medical achievements of the past half century. It remains in form and substance, with few additions and refinements, what

it was when the chief concern of hospital staffs was the frequent discrepancies between antemortem and postmortem diagnoses. We now have reached the point where, with the aid of roentgen-ray and clinical instruments of precision, these discrepancies are the exception rather than the rule, and emphasis is being forced increasingly upon functional rather than anatomical abnormalities. We are not satisfied to know only that an individual has organic heart disease but how he can live usefully and comfortably with it. The psychic factors in such illnesses as allergies, diabetes, hypertension, and arthritis assume more important rôles, not only in their management but in etiology, and the only means available to determine how much importance is to be accorded them in individual cases is an adequate medical history. It is not so much a matter of differentiating between organic and functional disorders as it is determining all the factors of a patient's disability.

In answer to the pertinent question as to what might be called an adequate history, Cobb [5] states, "The point is to get the story of the patient's present predicament as much in his own words and his own order as possible. If this is done it is much more likely to be true than a story elicited by a set of stock questions. Many neurotic patients, when put through the mill of a regular routine: 'Chief complaint, present illness, past history, occupation history, marital history, system review and habits' will react badly and say things that they do not mean, some of them actually untruthful and misleading. To get all this down in the record is harmful because it not only wastes time but biases later opinion."

For the past two years an attempt has been made by the writer to evolve a case record technic in which the patient's history would rank at least as high in intelligibility as its other parts. First, the patient is allowed to state his complaints in as much detail as he desires in his own words with interruptions only to keep him on the theme of his *present illness*. When his statement has been completed, information relative to *present* functions of the neuro-muscular, cardio-respiratory, gastrointestinal and genito-urinary tracts is elicited as necessary to supplement what he has given. Following this recital of his present complaints, he is asked to give in his own words his personal history beginning with childhood. With the information that most chronic illnesses, functional and organic, have their origins in the easily forgotten past, he is told that the history might be given in narrative form so that, through association, as many of the events of his life as possible can be brought into the picture. No attempt is made to make him disclose what he might choose to leave unsaid, but the information desired concerns his childhood experiences and illnesses; his status in home and at school; the social, economic, and medical status of his parents and his preference for either one; how he reacted to disappointments and affection; what progress he made in school; how and when he learned about sex and what was his reaction to this instruction. He is encouraged to tell about his love affairs, religious experiences, ambitions, etc., as he passed through adolescence, and, when adulthood was reached, about his economic, social, and marital life

as it had been lived up to the time of the consultation. His own and his family's illnesses are placed in their proper setting as the story is told. The objective is to get as complete a summary as possible of all the elements that might enter into the complaints that bring him to the doctor's office. The interview is kept on a voluntary level and the benefit frequently derived is not only a mutual better understanding of the causes of presenting symptoms and a basis for future additions to the story, but where the beginnings of hypertension, allergies, and other chronic diseases can be placed in their proper setting, a workable program of treatment can be set up with less difficulty than if a narrative history is not secured. Where there are major psychic factors beyond the internist's capacity to handle, reference to a psychiatrist can more easily be made. The time taken for such histories has averaged 30 minutes to one hour. The patient having an objective and the opportunity to achieve it has less incentive or inclination to ramble.

The practical application of this method of history taking in general practice may be illustrated by the following abstracts:

### Case Reports

*Case 1.* A 23 year old white male employed as a gang foreman by an insulating company complained of periodic attacks of chest pain and shortness of breath which began a year before and had been increasing in severity and frequency for the past five months. In the past week, he had three severe attacks while at work filling the walls of houses with insulating material and had to be taken home. A roentgenogram of his chest was taken and he was told his lungs were "full of wool." He also complained of a pain in his left eye and loss of libido.

He was born on a farm, the second of four brothers and sisters. His parents were easy going church people and he was equally fond of both. He had measles, mumps, and chicken pox before 11 years of age and German measles at 14. One day, when he was five years of age, he and his cousin were testing their eyes at play and he found he could not see as well with his left eye as with the right. This frightened him, and his parents took him at once to an eye specialist in a nearby small city who put "drops" in his left eye and made him wear colored glasses for several days. Thereafter, three or four times a month, for six years, this treatment was repeated. He liked the doctor, who gave him ice cream, but did not like to wear colored glasses because he could not read for several days after each treatment. One day he heard the doctor tell his father that he had an abscess behind his left eyeball. The boys at school teased him because of his glasses and he was three years getting around to taking care of his tormentors. When he was 11 he was fitted with glasses, the left one as "strong as his father's reading glasses." His doctor died and he wore the glasses until he "outgrew them." Later he went to another doctor in the same town who gave him a new pair. He did not wear his glasses all the time but needed them when he was tired or upset about his studies. He was very much interested in church and took part in all of its activities. He masturbated occasionally until he was 18. Then one night he had a date with a young lady who had a reputation among the boys. On their way home he saw two people crossing a bridge in front of them and he thought they were his father and mother. Thereafter, he had no sex affairs and stopped masturbating. After graduating from high school he worked with his father at home and noticed that when he was working in a dusty place his nose would stop up but he did not have any symptoms of asthma. A year later he got a job with his present employers and married a girl from his home town whom he

had known since childhood. They had been happy, had one child, and he had made a good living for his family. He had enjoyed his work which had been the same for the past two years. He first was directly associated with a member of the firm of whom he was very fond. When this person took over another part of the business out of town, he was assigned to work under a man with whom he soon began to have trouble about his pay. Then he noticed that he would tire easily and had times when he got out of breath easily and his eyes bothered him. For five months there had been several occasions when he did not get all the pay for overtime to which he thought he was entitled, and two weeks later he worked 13 hours overtime and was paid for only five. This resulted in an altercation with the department head which almost ended in fisticuffs. He did not want to say anything or do anything "unbecoming a gentleman" or tell his troubles to anyone except the member of the firm who was out of town. He felt that his boss was dishonest in other matters also, and, if given time, would eventually be found out.

His attacks of pain and dyspnea became very severe and occurred every day or two. The pains were sudden in onset, making him stay in one position and hold his breath. They lasted from one to five minutes—always localized in the anterior portion of his chest. They were knifelike in character, gradually subsiding and leaving him weak, dizzy, and sometimes nauseated. For several hours afterward, he was exhausted and nervous and unable to work. He had always worn a respirator at work. During this period he had difficulty getting to sleep at night, his appetite was poor, and he had contemplated consulting a physician because of loss of libido. His eyes throbbed when he read too long and he went to the city where he was first treated for a pair of new glasses.

A roentgenogram of his lungs showed heavy bronchial markings but no parenchymal change. Roentgen studies of his gastrointestinal tract showed moderate hypermotility but no evidence of diaphragmatic hernia or other disease. Physical and laboratory examinations were negative except for amblyopia and a positive intradermal test with dust extract.

He was advised to have a talk with the senior member of his firm who had sent him for his examination and who later transferred him to work with another man. In a few days he was free of pain, had no difficulty eating or sleeping, and his marital affairs gave no grounds for complaint.

*Case 2.* A young man of 21, a third year college student, complaining of rapid heartbeat and abdominal distention presented himself for a "check up." He stated that he had always been under a doctor's care because of a "heart condition."

He was the youngest of two sons in a prosperous family and had a normal social life at home and at school. His father had some sort of "heart trouble" ever since he could remember. He never saw him in any acute distress but said his father was a person who kept his troubles to himself. His mother was always solicitous about the health of the members of her family. He had the usual diseases of childhood and a tonsillectomy at six years of age.

From two to 11 years of age he lived in a small town and during one of his illnesses the doctor found a "murmur" when examining his heart. Thereafter, whenever the doctor saw him the doctor would stop where he happened to be, at home or elsewhere at play, and listen to his heart. He was always cautioned by the doctor and his mother to "take it easy."

He had no other illnesses but went occasionally to a doctor for "check ups." Each time he was told to "take it easy" and not get tired, and when a college physician told him he was in good health he felt that the doctor knew he wanted to go to college and would not stop him even though he had "a heart condition." He was examined for R.O.T.C. and later passed the army induction center where he thought the examiner was inexperienced and did not give him as careful an examination as

would a more competent man. His social history indicated no abnormalities and he stated that the only stress he had experienced had been his anxiety about his "heart condition" which he said he took as philosophically as possible and if he died of heart disease he "would not be any worse off than a great many others with the same trouble." However, he did not want to "do anything foolish" that might make his end come sooner than necessary.

He noticed that his heart beat rapidly during and after exercise and occasionally when lying quiet he had a "spongy feeling" in his precordium where there was also an occasional slight pain or "catch." After climbing a long flight of steps he became aware of a forceful pounding which subsided in one or two minutes. He had taken part in sports but always had been conscious of his heart and when it pounded forcibly he had always stopped what he was doing. He said he did not want to take a "morbid view of his incapacity." He also noticed that immediately after eating his abdomen became distended and he passed a great deal of gas by belching and by rectum.

Physical and laboratory examinations revealed no abnormalities and exercise tests were normal.

When it was pointed out to him that his heart behaved like the hearts of other men, he asked why then had he been told to "take it easy." Later he got assurance by comparing his heart action with his roommate's and doubted less the ability of the college and army physicians to identify heart disease.

These two cases illustrate the part played by early childhood experiences in the development of inadequate personalities. In the first case, the boy was handicapped for six years in his studies and in looking out for himself with his schoolmates. Thereafter, when in trouble, his attention became focused upon his physical disability and he retreated into a mild form of invalidism. When he grew up he had not learned to deal with adult problems and his autonomic nervous system response to stress was exaggerated to the point where it contributed to an incapacitating illness. In the second case, the young man in early life had been encouraged to identify himself with his father, who was said to have had heart disease, by repeated examinations of his own heart and the guarded solicitude of his mother and examining physicians. In neither instance could the most noteworthy factors in etiology have been brought to light by the customary methods of history taking.

The cases are presented for the single purpose of illustrating how the correlation of physical symptoms and emotional equivalents in a narrative medical history may give the general practitioner a serviceable instrument in physical diagnosis. It is not to be inferred that the subject matter of such histories includes all the information that is necessary for psychiatric care.

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# ANALYSIS OF ROENTGEN-RAY DIAGNOSIS IN CARCINOMA OF THE CECUM AND ASCENDING COLON *

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## Introduction

The value of roentgen-ray study in the diagnosis of carcinoma of the colon is well established. Clinicians have noted that a barium enema done routinely may reveal a carcinoma, even though the patient has no symptoms of a malignant lesion. On the other hand, there is a tendency to allow a negative barium enema report to rule out carcinoma of the colon even in the presence of suggestive clinical findings such as change in the bowel habit, abdominal pain, anemia, weight loss, fatigue, the presence of a mass, etc.

Hodges [1] states that the "x-ray manifestations of colonic neoplasm can be misinterpreted even by experienced observers trying diligently to make correct diagnoses." Bockus [2] states that "lesions in the flexures of the colon and those on the posterior wall of the caecum are liable to be missed" and that one should "studiously avoid a sense of false security given by negative reports made following barium enema study, particularly when there are clinical indications of malignant disease of the colon." Feldman [3] states, "In doubtful cases it is important to carry out repeated roentgen studies." The purpose of this paper is to evaluate the barium enema findings in the diagnosis of carcinoma of the cecum and ascending colon.

Whitehead [4] calls attention to the fact that one should resort to very careful fluoroscopic examination and frequent spot films to improve the accuracy of the diagnosis of carcinoma of the colon. Weber [5] emphasizes the importance of proper preparation of the patient before barium enema and advises double contrast examination. Schätzki [6] calls attention to the difficulty of differentiating diverticulitis from carcinoma of the colon and the importance of preservation of mucosal folds in making the differentiation. Case [7] cautions against overfilling of the terminal ileum, since, with overfilling, coils of the ileum may interfere with the post-evacuation study. He also states that a well-trained and experienced roentgenologist should succeed in identifying malignancy of the colon in 90 per cent of the cases. Morrison [8] advises that in order to continue below a 10 per cent failure in roentgen-ray diagnosis, the radiologist should be given a complete history by the physician. He also states that adequate preparation is imperative and re-

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peated examinations should be made if symptoms persist after a few weeks of treatment.

Because of the peculiar anatomy and character of pathological changes of the cecum and ascending colon, several facts concerning roentgen-ray diagnosis of carcinoma of the cecum and ascending colon should be noted. First, since the cecum is most distant from the anus, the cleansing enema is less apt to be effective in preparing the cecum than in preparing the rest of the lower bowel. Second, the cecum and ascending colon are larger in diameter than the remainder of the large intestine. Because of this fact, a lesion in the cecum or ascending colon does not usually produce obstruction as early as a malignant lesion elsewhere in the large bowel. This lack of evidence of obstruction makes the diagnosis more difficult. Third, because of the size of the cecum and ascending colon, it is easier to overlook a filling defect here than in the rest of the large intestine. This is particularly true when the filling defect is on the posterior wall. Fourth, carcinoma of the cecum or ascending colon is apt to be polypoid, producing late symptoms, signs, and roentgen-ray findings. In summary, carcinoma of the cecum and ascending colon are usually more difficult to diagnose by barium enema studies than carcinoma of the more distal lower bowel.

## Method

All roentgen-ray examinations were done by the personnel of the Roentgenological Department of the Henry Ford Hospital. The patients were prepared for examination by purgation with castor oil the evening before, and by taking a saline enema the morning of the examination. It was a routine procedure to do a careful fluoroscopic examination before taking the barium enema film. Spot films and double contrast films were done in some cases and evacuation films in others. All cases included in this study proved to have carcinoma of the cecum or ascending colon by biopsy studies at operation.

## Results

The time interval between examination and operation is important. Of the four negative examinations, all examinations were done within six weeks of operation. Of the eight cases requiring two examinations, in two cases the first examinations were done six and seven months prior to operation; in the remaining six cases, the first examinations were done within one month of operation. In the two cases requiring three examinations, in one case the examinations were done six weeks, two weeks, and five days before operation; in the other case, examinations were done six months, five and one-half months, and one week before operation.

Table 1 shows that the diagnosis was made on the first roentgen-ray examination in 36 cases. Repeated examinations were done upon 10 cases either because the first examination was unsatisfactory owing to poor prepa-

TABLE I

Diagnosis of Carcinoma of the Cecum and Ascending Colon from Barium Enema Examinations

| | Number of Cases |
|---|---|
| Diagnosis of organic lesion on first examination | 36 |
| Diagnosis of organic lesion on second examination | 8 |
| Diagnosis of organic lesion on third examination | 2 |
| Negative examination | 4 |
| Poor preparation, not repeated | 2* |
| Total number of cases | 50 |

* In these two cases no diagnosis was made because of poor preparation and the Roentgenological Department suggested repeat examinations. However, the clinical findings and urgency of operation prevented this. Since the barium enema examination was not satisfactory and repeat examination was recommended, these two cases are not included in our percentages.

ration of the patient, or because the clinical findings were so suggestive of a malignant lesion that the clinician was not satisfied with one negative roentgen-ray report. On the repeat examinations, the malignant lesion was diagnosed in these 10 cases. Consequently, roentgen-ray examination was diagnostic of an organic lesion of the cecum and ascending colon in 46 out of 50 cases, or 92 per cent, of carcinoma of the cecum and ascending colon. Two patients operated upon before repeat barium enema examination could be carried out are not included. Table 1 illustrates the importance of repeating the examination when the patient is poorly prepared, or when the clinical signs are suspicious of a malignant lesion of the cecum and ascending colon. It also shows the importance of close liaison between the roentgenologist and the clinician.

Careful coöperation between the clinician and roentgenologist is of great value in arriving at a successful diagnosis and in determining when a repeat examination should be done in the event of a negative report. The two cases in which the examinations showed only poor preparation might have shown the malignant lesion with repeat examination after better preparation of the patient.

Some of the examinations reported in table I were done before the use of evacuation and double contrast films and spot films. It is believed that these new technics should improve the accuracy of diagnosis of carcinoma of the cecum and ascending colon.

TABLE II

Type of Defects Found on Barium Enema Examination in Carcinoma of the Cecum and Ascending Colon

| | Number of Cases |
|---|---|
| Total number diagnosed | 46 |
| Filling defect | 32 |
| Irregularity | 24 |
| Narrowing of lumen | 8 |
| Obstruction to barium | 7 |
| Small bowel obstruction | 6 |
| Intussusception | 1 |

Negative examinations were obtained in four cases. One of the four cases had two barium enemas because of the strong clinical impression of malignancy of this area. In one of the four cases a diagnosis of an extrinsic lesion deforming the cecum was made. The error in diagnosis was less than

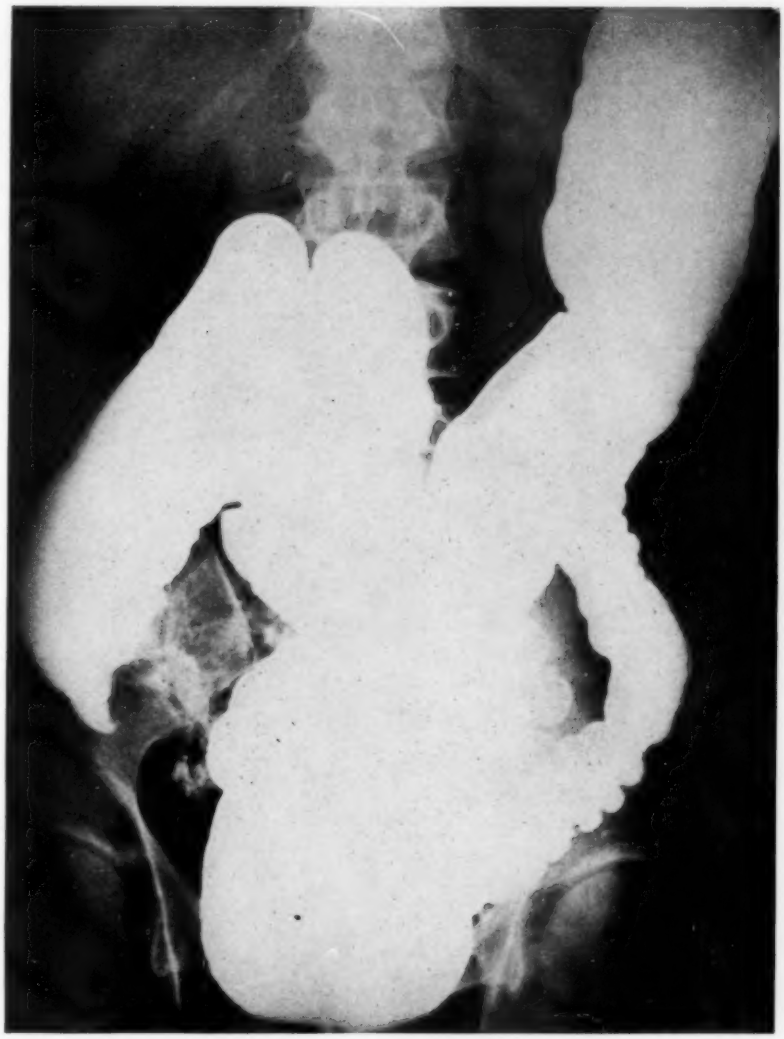

FIG. 1. Barium enema of carcinoma of the cecum showing filling defect in the cecum.

10 per cent and corresponds generally with the margin of error observed elsewhere in the diagnosis of carcinoma of the colon. We believe that an 8 per cent error in the diagnosis of a malignant lesion of the cecum or ascending colon is fairly low.

From table 2 it is apparent that a filling defect was present in 32 cases

and was the most common roentgen-ray finding. Irregularity was present in 24 cases. Eight cases had a narrowing of the lumen, seven had obstruction to the barium, and six cases had small bowel obstruction. One patient had definite evidence of intussusception.

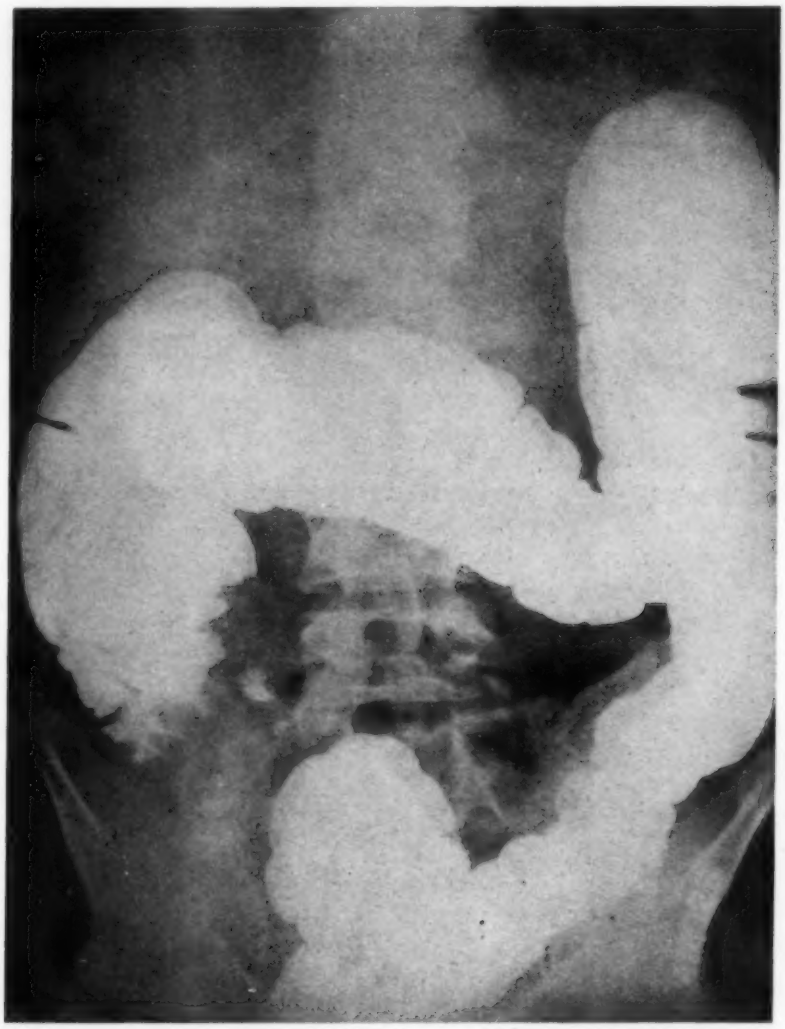

FIG. 2. Barium enema of carcinoma of the cecum showing filling defect, irregularity, and partial obstruction at the ileo-cecal valve.

Two cases were difficult to diagnose because the cecum was redundant and low in the pelvis, making palpation difficult. It is important that overfilling of the colon and ileum be avoided in the examination, since loops of the ileum then may obscure the cecum.

Examples of the type of defects listed in table 2 are seen in figures 1 to 4.

SUMMARY

The barium enema examinations in 50 cases of carcinoma of the cecum and ascending colon, proved at operation by biopsy, were analyzed.

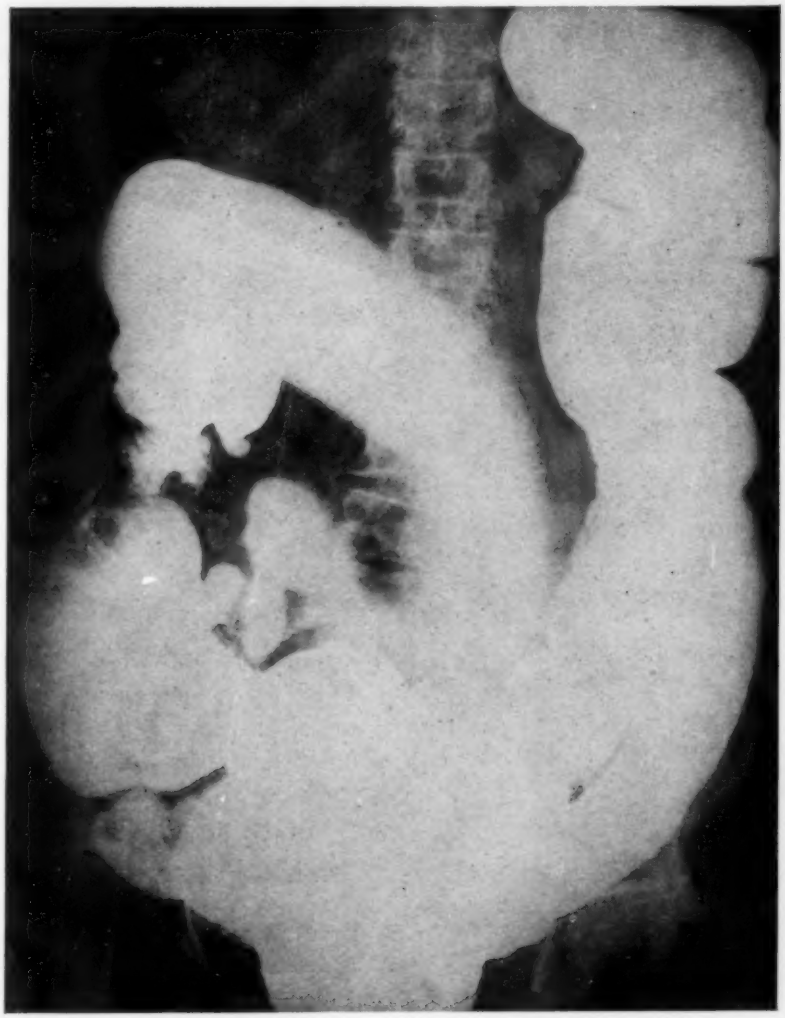

FIG. 3. Barium enema of carcinoma of the ascending colon showing narrowing of the lumen and a constricting lesion of the ascending colon.

The roentgen-ray diagnosis of carcinoma of the right side of the colon is more difficult than the diagnosis of carcinoma of the left side of the colon because (1) the cecum and ascending colon are more difficult to prepare for examination, (2) carcinoma of the cecum and ascending colon is less apt to produce an annular constricting or an obstructive lesion, and (3) because

the size of the cecum and ascending colon frequently makes it easier to overlook a small filling defect.

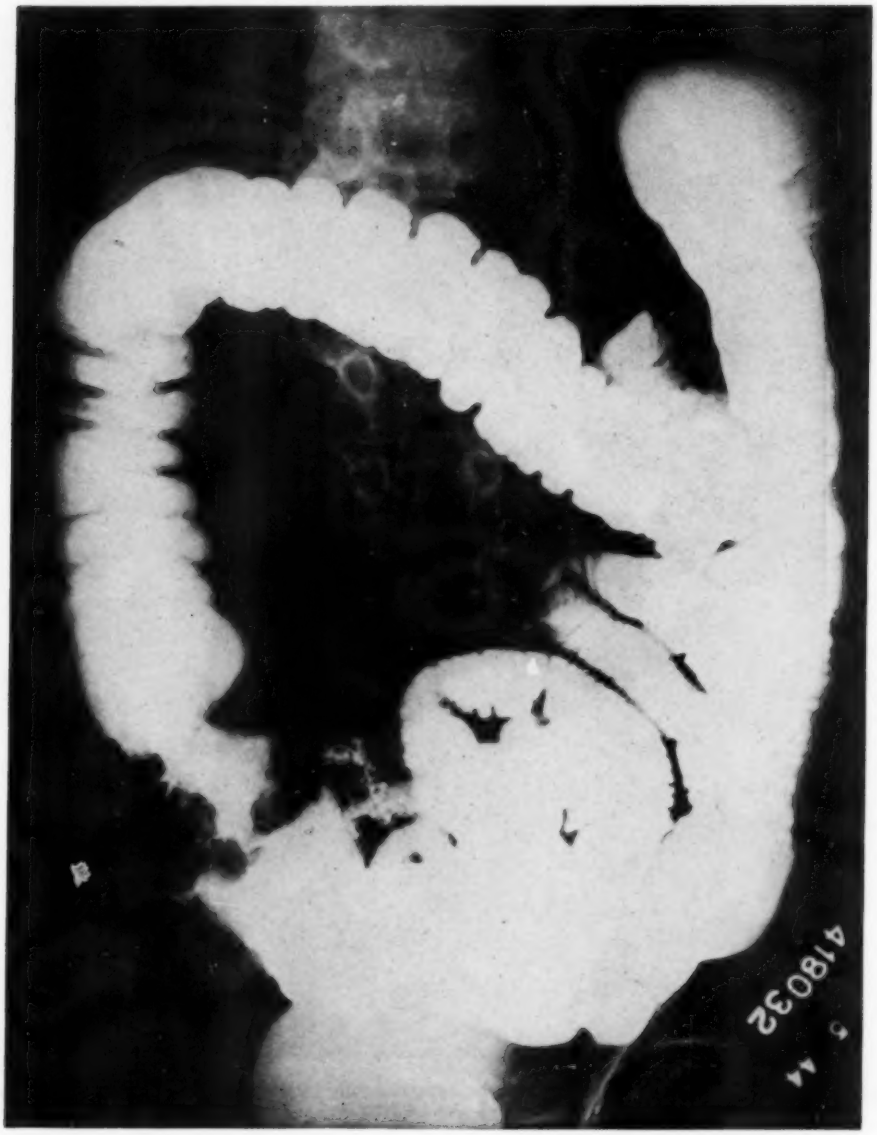

FIG. 4. Barium enema of carcinoma of the ascending colon showing narrowing and irregularity of the ascending colon.

Correct diagnoses were made in 36 out of 50 cases, or 72 per cent, on the first examination. Ten patients, or an additional 20 per cent, had to have a repeat barium enema before a diagnosis was made. The reason for

the repeat examination in some cases was poor preparation for the first examination; in other cases the repeat examination was done because of clinical evidence of a malignant lesion in that area. The patient must be well prepared for the barium enema study if carcinoma of the cecum or ascending colon is to be ruled out. Even with good preparation and a negative report, the examination should be repeated if there is any clinical evidence of a malignant lesion in this area.

With careful examinations, and repeat examinations whenever indicated, the error in diagnosis of an organic lesion in this area should not exceed 10 per cent. The barium enemas of four, or 8 per cent, of the proved cases of carcinoma of the cecum or ascending colon in this series of 50 cases were reported as negative for an organic lesion of the cecum or ascending colon.

The most common diagnostic roentgen-ray findings were filling defects and irregularities, which were present in 32 and 24 cases respectively. Narrowing of the lumen was present in eight cases, obstruction to the barium in seven cases, small bowel obstruction in six cases and one case had evidence of intussusception.

## Conclusions

Roentgen-ray diagnosis of carcinoma of the cecum and ascending colon is often difficult.

Good preparation for the examination is necessary. The examination should be repeated if there is any question about the preparation.

Even with good preparation and a negative barium enema study, the examination should be repeated if there is clinical evidence suggesting a malignant lesion in the area.

With careful technic and preparation, using fluoroscopy and films, and doing repeat examinations whenever indicated, the error in roentgen-ray diagnosis of an organic lesion of the cecum and ascending colon can be kept at 10 per cent or less.

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# PROTECTIVE REACTION PATTERNS AND DISEASE*

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AN ancient awareness of the linkage of feeling and bodily changes is borne to us in the heritage of our language. Applied to the vasomotor system we have such phrases as "red in the face," "hot under the collar," "pale with rage," "being in the pink of condition"; applied to respiration—"takes one's breath away," "sighed heavily with passion," "his nostrils dilated with rage"; applied to perspiration—"went into a cold sweat," "cold hands, warm heart," "he has cold feet," "dripping with suspense"; applied to the gut—"it's a nauseating experience," "it makes me sick," "it turns my stomach," "I can't swallow that" "it's a gripe." In Henry VIII, Shakespeare refers to Woolsey as a man of "unbounded stomach." When referring to a frustrating situation it is said in current slang, "it is a headache." We say, too, in reference to pilomotor functions, "his hair stood on end," "it made his flesh creep"; in reference to skeletal muscle—"he's a pain in the neck," "he trembled with fear," "he shook with rage," "he had jitters," "he's a stiff necked fellow," "he became weak with laughter," "keep a stiff upper lip"; as applied to cardiovascular apparatus—"faint heart ne'er won fair lady."

The relevance of such bodily changes to disease has been brought into focus only recently, mainly because it has not been clear that these functional alterations may be profound or sustained enough to be of clinical significance. But now such sustained bodily alterations connected with varying life situations and emotions have been observed and recorded and to consider their pertinence to disease and tissue damage is the purpose of this essay.

*Development of Concepts.* We have been encouraged by our teachers to abandon dualisms and dichotomies such as are exhibited when body and mind are used as opposing terms, and to develop a unitary concept of man. Such sound counsel has led to attempts at formulation, but our teachers have left us little data or language with which to proceed.

Darwin, Pavlov and Cannon attempted unitary concepts of behavior, but because of lack of information and tools, as well as because of the orientation of their times, the results, despite their importance, are limited. Thus Darwin, in his remarkable essay "Expression of Emotions in Man and Animals," has concerned himself relatively little with internal bodily reactions or with the analysis of drives. However, his detachment and curiosity about human behavior were a basic impetus to all later study. In tracing the humble origin of man and in discovering in his patterns of expression, links with his ancient past, he ploughed the ground for Freud.

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The demonstration by Pavlov that a given stress situation produces in the dog reactions of a highly individualized character based on the nature and experience of the particular animal, has had important implications for human behavior problems. Very significant, also, is the demonstration that such psychobiological stress can produce not only severe, but long lasting disorders of function.

The initial effect of Pavlov's data was an actual slowing of the progress of the study of man through the implication that it was unnecessary or even pernicious to use his own unique qualities of language and self-awareness. But soon it became apparent that sound scientific principles can operate in work with symbols as well as in experiments with more measurable components such as secretion and contraction. Thus, through the study of quantitative aspects of conditioned reactions in the dog, human behavior, hitherto considered "too complex" for the scientific method, became a subject matter for science.

Cannon had the courage and imagination to arrange the isolated and detailed phenomena of neurohumoral functions into an integrated pattern of emergency reaction, seen as mobilization of the animal's responses for fight or flight. Though this concept failed to distinguish between various kinds of protective reactions and took little account of varieties of feeling, it nonetheless emphasized the existence of a protective reaction pattern.

Exploring in other fields, Janet, Morton Prince, Freud, and Jung (notably Freud), formulated the concept of unconscious mental activities. Accordingly, the phenomena of mentation and behavior are conceived as the result of the interaction of a number of drives. These drives, which are in part conscious and in part unconscious, may work harmoniously together, or conflict with one another. In the latter case attempts at adjustment occur. Certain of these attempts involve the repression of one of the opposing forces, which then is no longer allowed to manifest itself in consciousness or in action. It becomes unconscious, but does not thereby cease to exist. It remains capable of functioning. It can no longer influence thought and behavior in a direct manner, but instead produces various indirect effects. This conception has illuminated our understanding of attitudes, feeling states, preferences, prejudices and decisions. But feeling states and behavior patterns were not correlated with other bodily reactions by these investigators.

Adolph Meyer, in the spirit of American pragmatism, saw man as a unit of function within the framework of general biology. No organism, he pointed out, is a mere accumulation of its component parts, but rather by virtue of complex interaction new potentialities occur, the nature of which can never be understood by analysis of the parts. Meyer taught that mental function, or mentation, is not to be regarded as a unique or detached process, but only as a special kind of functioning made possible by the particular integration of man's makeup; that man is a set of functions integrated into an adaptive unit called a "personality"; and that a discipline, which Meyer called psychobiology, could be developed which would study the human being

as a functioning entity. Meyer was primarily concerned with the shaping of his concept and only secondarily with the experimental demonstration of its fruitfulness. Hence his effort has influenced thought less rapidly than might otherwise have been possible.

At the moment, the bodily alterations connected with varying life situations and emotions are viewed in a variety of ways, each of which has its adherents. One is that the changes occurring in association with various feelings are meaningless, fortuitous, haphazard, and in a sense chaotic. They play no essential part in the reaction, but are seen as the outcome of a diffuse excitation within the central nervous system inducing effects in blood, smooth muscle, gland and skeletal muscle.

A second view presents the bodily alterations as manifestations of special anatomic peculiarities of the individual, and considers that certain individuals, during duress, incite activity within their sympathetic systems predominantly, whereas others do so within their parasympathetic systems. The responses are looked upon as resulting from excitation which, respectively, affects adrenergic or cholinergic fibers, but no other meaning has been imputed to these changes. This implication that a defect, either congenital or acquired, exists in one of the parts of the nervous system, giving rise to over- or under-activity, is akin to the view held by others that certain individuals are equipped with inferior organs which, under stress, break down, i.e., the stomach in dyspepsia. The defective functioning of the inadequate organ would thus add to the load put upon the man.

A third view (which to me seems more useful) looks upon the bodily changes occurring with various adverse life situations and accompanying emotions as not haphazard nor as evidence of organ inferiority, but as part of an arrangement or pattern, in which is integrated as much of the organism's equipment as is needed for a particular protective effort. It is implied that smooth muscle, gland and skeletal muscle functions, feeling states, attitudes and emotions are linked and have direction, although this direction may be at variance with the conscious purposes of the individual.

When assaults and threats are squarely faced by the individual, and elicit prompt action, the self-protective pattern in his behavior is clearly seen. Thus, a boy avenging an insult by hitting hard in fisticuffs uses a necessary part of his protective equipment to deal with the assault. Less obviously related to environmental stimuli are patterns of protection evoked unconsciously, when drives unacceptable to the individual are repressed. These drives may be touched off by symbols often unrecognized. For example, a man, after being subjected to a lifetime of destructive domination by his mother, cannot allow himself to strike her, nor even to feel anger toward her. An apparently neutral incident can arouse his hostility but his evoked anger is repressed. Such drives continue to affect behavior, but since they are barred from awareness, the protective patterns evoked may be only atavistically relevant to the situation. For instance, increasing the heart rate to improve circulation is a primordial response for fight or flight, but tachy-

cardia cannot regain love for a rejected spouse. Nevertheless, the protective patterns evoked may be specific in character, indicating efforts to get rid of, to shut out, to fight or to flee.

These patterns become medically significant when they are prolonged, since irreversible changes and tissue damage may ensue. Hence duration is of prime importance. When the individual's reactions are on the conscious level, his protective patterns serve their purpose and usually are promptly dissipated. However, under certain circumstances the need for them may be prolonged, as during exposure to sustained adversity or to a series of threats in battle. Also, because of unusual sensitivity based on special experience the individual may over-react to relatively minor assaults and thus protective patterns persist for long periods. Furthermore, when, due to conflict and subsequent repression, an individual's reactions are out of awareness, the unconsciously evoked protective patterns may persist as long as the repression lasts, which may be for years. The resultant picture is one of antagonistic purposes and contradictory behavior, since contrary drives are being expressed. Within each pattern, however, behavior and bodily reactions are consistent and protective in aim.

There are many such protective patterns, both defensive and offensive. It is likely that the neural processes involved in conditioned reactions are operating in these behavior patterns, but at the moment it is more profitable to consider behavior in broad biologic terms. Any one organ or system may participate in either defensive or offensive patterns. A few of these patterns will be touched upon here, and the first to be considered will be an offensive protective pattern, involving assimilation.

*Protective Patterns of Offense Involving Eating—the Stomach and the Duodenum.* Direct observations were made possible by Tom who came to us with a large abdominal stoma. This man, now 59 years old, came home one night when he was a child aged nine, thirsty and hot after playing in the streets. Finding on the back of the stove a large beer can filled with what he thought was cold beer, he grasped the beer can, took a large mouthful of the hoped-for cool, frothy stuff, but instead he had to swallow scalding hot clam chowder. During the next few months many attempts were made to expand his partially occluded esophagus, but with the passage of time it became apparent that this was not going to be possible. He was then brought to the hospital malnurtured and in terror.

The surgeon planned to make a small stoma through which to feed the child and ultimately to close the stoma after suitable arrangements had been made in the esophagus. For various reasons, however, the child did badly at the operating table, and the operation had to be hastily concluded. So instead of getting a small stoma, this child was left with a large opening and a generous collar of mucous membrane on the outside. This man grew up, worked, got married, had children, and conducted himself as a responsible citizen for the next half century. He is a shy, sensitive, lively little man, quick to anger, quick to forgive, unschooled, responsible, overly conscientious.

He became a diener in our laboratory and the plan was that he'd come in every morning without having breakfasted, put himself on a table, and allow us to look into the stoma. After preliminary observations the important events of the last 24 hours, his attitudes about them, whether things were going well at home, what his feelings were, would be discussed. Tom is a "man of few words" but he is nevertheless articulate in the sense that sooner or later you know exactly what he feels. He has the ability to communicate.

To round out a rather small salary, this man cleaned the apartment of a member of the medical school staff. Tom did not know much about cleaning apartments and he was slow, ineffective, and costly in terms of the help available at the time. So my associate planned to "fire" him. This was done under laboratory circumstances. When he discharged him, he told Tom about his deficiencies. Tom got red in the face, saying, "Yes, Sir," "No, Sir," not expressing his anger in words, but exhibiting it by color changes in his face and stomach. When my associate left, Tom was "boiling with anger" and said, "I could choke that man," as a final comment on the subject. During the words of dismissal, the gastric mucosa got red (increased blood flow), the hydrochloric acid secretion and motility increased.

Here, then, is a response of peptic hyper-functioning, with anger, conflict, resentment, which may last a matter of minutes or days or weeks. Usually Tom quickly "blows his top," and then his anger is ended. The situation may be sustained for a few days or weeks, however, and the stomach hyperfunction may be likewise sustained. Thus Tom had a benefactor who gave him a certain amount of money to round out his small income. Tom resented his benefactions because, like many benefactors, this one felt free to meddle in Tom's personal affairs and tell him how to spend his money. He was not being deprived of love or security, but was being deprived of exercising his right to live in his own way. Following a visit from his benefactor, the stomach had a high color and was hyperacid. This persisted for two weeks, and was dissipated by raising Tom's salary and enabling him to throw off his benefactor. Tom's gastric reaction to threats is characteristically one of hyperactivity, just as his way of meeting an adverse life situation was to take active steps to correct it.

When there is a high color in the exposed mucosa, the tissue bleeds easily, due probably to the increased fragility of the distended minute vessels. After sustained resentment, one may see many small hemorrhages, scattered here and there over a wet, hot-looking, shiny, engorged mucosa. When tranquility is reëstablished and the situation is left to itself, the hemorrhagic spots spontaneously disappear although the mucosa may remain edematous for some days. If one interferes in any way with the protective action of the mucus, say, by removing the mucus and putting a little wall of petrolatum about such a spot and then allowing the gastric juice, with its hydrochloric acid and pepsin to act on the unprotected surface, an ulceration can easily be produced. However, when the mucus is again allowed to protect that area,

within three days there is no sign of a lesion. During the period of noxious stimulation of the mucosa by the action of the gastric juice there is a vicious cycle started in which both blood flow, color, and acid production are increased. So, once the lesion is started, a self-perpetuating cycle, due to the presence of the lesion and noxious stimulation, is established.

What has been observed in Tom is relevant to others. In a patient with peptic ulcer studied by conventional methods, we have seen various levels of gastric acidity at different times; a low level was associated with a period of relative security, a high one with extreme insecurity in which the patient was being pursued by the police. He is a professional beggar, and begging in this instance is part of a pattern of "getting even" with society for injuries that he sustained as a child and as an adult. He insisted on coming into the hospital via the private entrance and then coming up in the private patient's elevator. The doorman knew of our work with him and never interfered. However, on one particular day the patient found a stranger at the door, a substitute doorman who, not knowing our subject, sent him to the back entrance, so to speak, and up to our laboratory via the Out Patient elevator. The man entered the laboratory in a humiliated, angry state, and with a small amount of fresh blood in his stomach. This was appreciably increased during the interview about his recent experience. When, after a few minutes, the topic was rediscussed, bleeding was renewed. Whether this was bleeding around the already existing ulcer or the breaking up of a small blood vessel elsewhere in the now engorged mucosa, is not clear, but it is evident that this man's protective reaction to an adverse situation, like Tom's, includes the stomach.

Thus, one of the earliest aggressive patterns to manifest itself in the infant, namely, that associated with hunger and eating, may, in certain individuals, in later life, when the organism is threatened, reassert itself. At such times of anger, the feeling itself, the demand for emotional support or insistence on being cared for may be repressed by the equally insistent assertion that the individual is strong, independent, capable of doing alone, of standing on his own feet. Either through actual deprivation of support or an unwillingness to accept it, this angry, hungry state shows itself in the stomach as one of readiness for eating.

The hyperdynamic state of the stomach first becomes associated with symptoms arising from excess motility, engorgement and hyperacidity and this may be followed by damage of the gastric mucosa. It is the conflict between two goals, one not clearly stronger than the other nor yet in agreement. A conflict between two parts of a man expressing "I want" and "I won't let myself have," or "I want and I can't get it." The reaction pattern expresses divergent goals, now one now the other, sometimes both at the same time. The animal appears unable to resolve the dilemma created by his conflicting drives and in the struggle digests his own gut. In essence, the activities of this man in dealing with his day to day problems took the form of offense. Even though "an humble beggar," his aggressive acts took the

form of childish temper outbursts (perhaps because the infant is an angry beggar when hungry). It was possible to demonstrate in another fistulous subject studied before and after vagotomy that the vagus nerve was the principal neural pathway involved in vasomotor and motility changes associated with gastric hyperfunction during conflict and anger.

*Protective Pattern of Defense: The Ejection-Riddance Reaction Involving the Large Bowel, the Stomach and Duodenum.* Many infants during the onset of infection vomit and have diarrhea in reaction to the invasion of a noxious agent even when the gastrointestinal tract is not primarily involved. Hence, during a fretful, irritable, uneasy state the feverish infant attempts to protect itself by ejecting that which it has inadvertently admitted. Usually before adolescence the child abandons the non-specific and inappropriate reaction to assault, utilizing it sparingly to rid itself of noxious agents actually present in the gut. But some adults persist in the inappropriate use of the ejection-riddance pattern, even when the assault has nothing directly to do with the gut. A subject actively participating in the environmental demands made upon him, but finding himself inadequate to deal with them may elaborate a pattern of ejection. Thus, a person who has "taken on more than he can handle" or feels inadequate to the demands of his life situation, or a thwarted person filled with hatred, defiance, contempt and the unconscious aim to eject a threatening or overwhelming situation, may have diarrhea. However, the riddance pattern being integrated through unconscious processes, the subject exhibiting violent diarrhea may be calm, sweet mannered, and even serene.

Almy, studying subjects with hyperirritable large bowel and mucous colitis, found hypermotility and a bright red mucosa secreting excessive mucus. It would appear as though the large bowel functions under the circumstances of ejection in a manner different from that of the stomach. The latter is pale and hypomotile, though it contains much mucus. (S. Wolf).

Our subject, Tom, with the large gastric fistula, revealed that an agent such as ipecac which, because of its toxicity, threatens survival, or "Amigen" or "Amphogel" which because of their texture, taste or other unesthetic qualities were unacceptable or revolting, elicited anorexia, feelings of nausea, and often precipitated into action the duodenal and skeletal muscle patterns of vomiting. The motility and tone of the stomach diminished, the acid secretion dropped dramatically, and the gastric mucosa became pale. However, the mucus secretion increased, and subsequently vomiting occurred. Such an increase in mucus secretion is compatible with the view that the noxious agent might be diluted, neutralized, or washed away. This, coupled with a motor pattern which empties the stomach through the esophagus and mouth, would be maximally effective in protecting the organism against an ingested poison.

It also became evident that unacceptable or offensive situations, or those eliciting feelings of disgust, were likewise associated with sensations of nausea, increased secretion of mucus, and depressed digestive function.

Also with the increased mucus secretion in the stomach, salivary secretion increased. Under these circumstances, Tom and other subjects complained of anorexia, distention, gastric fullness, belching, retention of food in the stomach, "dyspepsia" and ultimately vomiting. Thus, situations which the individual found unacceptable either because of their poisonous pharmacological effect, or because they otherwise constituted a threat or assault to his security, were associated with a defensive protective reaction involving dilution, neutralization and rejection and ejection.

This is exemplified by a woman aged 24 who came to the New York Hospital complaining of fullness in the epigastrium associated with anorexia and nausea. She had been rejected by both parents, had reacted to life problems with indecision and had attempted to resolve them by rationalization rather than action. However, she did join a world movement. She felt that her own security and that of the Jews in general depended heavily upon the success of the Zionist movement. She was intubated with a gastric balloon and with another tube through which specimens of gastric juice were collected. The balloon was inflated in the stomach and connected to the kymograph. During a phase of gastric contractions of average size and frequency, her attention was called to a newly formed society dedicated to opposing the Zionist movement and exposing what they considered misrepresentations by the Zionists. She had not previously heard of the society, and she appeared disgusted and horrified to learn of its activities. She stared, pale and wide-eyed at the examiner, immobile and obviously frightened. The motor activity in her stomach promptly stopped and the organ relaxed and increased in size. Finally nausea occurred. Later discussion revealed that this individual characteristically reacted to threatening situations with anxiety in which there were strong feelings of disdain, hopelessness and despair. "When something comes up to worry me, I have a feeling of being defeated, that things are hopeless. That is how I felt when you showed me that advertisement of the anti-Zionist organization."

Akin to this, but somewhat different in their effect, were situations that were considered overwhelming and induced feelings of dejection, sadness, grief, abject prostration, despair, horror or defeat. These were associated with absent or decreased gastric motility and tone, delayed emptying and hypo- or anacidity, with pallor of the mucous membrane. Mucus and salivary secretion also diminished, and gut contractions were diminished or absent. The following account is an example of such depression of gastric function in association with fear and sadness.

Tom suddenly experienced intense fear one morning in the midst of a phase of accelerated gastric function. An irate doctor entered the room muttering imprecations about an important protocol which had been lost. The subject had mislaid it and expressed by talk his fear that he had lost the record and his job. During the ensuing minutes while the doctor was opening and closing drawers, Tom lay motionless on the table and his face became pale. Prompt and decided pallor occurred also in his gastric mucosa,

and was associated there with a fall in the rate of acid production. A minute later, the doctor found his missing protocol and left the room. Forthwith the face and gastric mucosa of the subject regained their former color.

Sadness, dejection and feelings of self-reproach were accompanied in this subject by taciturnity, lack of "energy", slowness of movement of the body generally and by pallor of the gastric mucosa, decreased acidity and gastric motor activity. Even the stomach's normal response to the ingestion of food was inhibited under these circumstances. Thus, one morning, the subject was depressed and uncommunicative over having lost, through his own negligence, an option on a house which he had long been eager to acquire. He was limp and dejected and filled with feelings of self-depreciation and refused to relate the nature of his trouble until several hours later. Beef broth was administered directly into his stoma and it was noted that the hyperemia and acceleration of acid production and motility, which regularly followed ingestion of beef broth, were partially inhibited.

A similar gastric and feeling pattern occurred when a beloved member of his family died. Other subjects were found characteristically to meet threatening or adverse life situations with feelings of defeat and dejection. These were predictably accompanied by depression of gastric activity.

It would thus appear that situations or symbols which, because of their significance to the individual, cause him to feel overwhelmed, or evoke feelings of desperation, are associated with the almost complete cessation of gastric activity. This is compatible with the view that the blow has shocked the organism and evoked an emergency pattern, in which digestive function is irrelevant and is therefore abolished.

In brief there would appear to be two varieties in the pattern of gastric hypofunction which are closely linked and which often co-exist.

1. A pattern associated with overwhelming catastrophy with feelings of fear, terror, horror, abject grief, depression and despair in which practically all gastric function comes to a standstill.

2. A pattern associated with threats or assaults that elicit feelings of disgust, contempt, or which, because of the personality and early experience of the subject, elicit patterns of ejection. In this protective reaction of defense gastric function is also reduced, but mucus production is increased as is also duodenal motor function, and the concomitant skeletal muscle contractions seen in vomiting result, again the organism behaving as though the noxious incident inadvertently ingested, could be diluted, neutralized and ejected.

*Protective Patterns of Defense: (a) Involving ventilation and the airways.* Protective reactions are also elaborated about the airways. Functional alterations in the structures of the nose have been studied and correlated with a wide variety of circumstances. These include noxious stimulation inside the nose by chemical agents, noxious stimulation of other portions of the head, variations in environmental temperature, interruption of afferent

nerve pathways, and numerous threatening life situations with their accompanying affective states.

In general, two patterns of disturbance of nasal function were recognized. The first involved vasoconstriction in the nose with shrinkage of the membranes and increase in the size of the air passages. Thus, a young man whose wife was soon to bear their first child, was terrorized when she coughed up much bright red blood. He brought her as quickly as possible to the hospital, dreading lest another hemoptysis occur, lest this symptom mean tuberculosis, long hospitalization, ruination of his life plans. Upon arrival at the hospital his nasal structures were observed to be pale, shrunken and dry. Opening of the airways allows of increased ventilation and is part of a mobilization pattern of offensive nature to be discussed below. Such changes accompanied feelings of being overwhelmed by fear or terrorized, which, however strong, involved minimal conflict.

More pertinent to this discussion of defense reaction was the second type of disturbance in the nose characterized by an initial hyperemia associated with turgescence of the erectile tissues in the turbinates and nasal septum, engorgement of the nasal mucosae and increased secretion. These phenomena occurred in reaction to local noxious stimulation on the mucous membranes and in the vicinity, and, as well, to other threats inducing significant conflict with resultant anxiety, resentment, anger, guilt and feelings of frustration. Thus, following noxious stimulation of the mucous membranes of the nose by fumes of ammonium carbonate, there was observed local hyperemia, swelling of the turbinates and increased mucus secretion. These changes were accompanied by obstruction to breathing. Also, immediately following inhalation of pollens the resultant "allergic" rhinitis in a sensitive man involved marked vasodilatation in the nose with redness of the membranes.

Noxious stimuli not directed at the respiratory passages, including painful stimulation of the head, induced similar nasal hyperemia with swelling, hypersecretion and obstruction. Special interest is attached to nasal changes which were found to be associated with conflict and with feelings of frustration and resentment and which often accompanied frank weeping or a state of being on the "verge of tears." There occurred initial redness of the mucous membranes of the nose, with extreme swelling of the turbinates and nasal mucosae, profuse secretion and obstruction. Complaints of difficulty in breathing ensued.

In general, hyperemia, swelling and hypersecretion in the nose were found to parallel one another, although after the establishment of swelling the hyperemia might subside, leaving pale, edematous, wet nasal structures. As previously observed in the skin, stomach and bladder, the turgid, hyperemic membrane of the nose was often found to have a lowered pain threshold. When threatening life situations productive of conflict were sustained, the associated nasal changes which might at first have been predominantly unilateral, became persistent and bilateral. Moreover, when swelling and ob-

struction persisted, pain and tenderness occurred and spread over the zygoma and into the temporal region. An example of such a defense reaction in the nose, and in the throat and chest as well, is as follows:

A 36-year old housewife complained of attacks of dyspnea, associated with dry cough and wheezing for the previous six months. Her parents were Russian Jews who came to America before the First World War. The father was lettered and gentle, the mother unschooled and cold; both were forceful characters. Her three sisters were married to Jewish businessmen, and the three brothers were successful as an accountant, a factory foreman and a lawyer respectively. They all enjoyed the favor of the parents, whereas the subject had incurred their disapproval by marrying a relatively non-competitive Roman Catholic of French-Italian parentage, nine years her senior.

She had been a bright, fun-loving girl who was nevertheless sensitive and wept readily. Because of precocity, she was advanced rapidly in school. She graduated from high school at the age of 16, but could not enter Normal School because she was too young. She was discouraged from becoming interested in young men by her family who told her she was too young. She was pressed to interest herself in study and shun youthful diversions. Nevertheless, at 17 she met and fell in love with a young Jewish lawyer, who resembled her father. The patient stated that he would not make love to her because he said she was "too pure and too young." In a rebellious mood she married a romantic and colorful Aryan; she looked earnestly to her husband for achievements to vindicate her defiant desertion of the family pattern. However, he obtained a job as a municipal garbage truck driver and had sharply limited aspiration. Her mother-in-law interfered in the conduct of her household, saying she was "too young" to manage her affairs. The patient ate excessively and became obese. Her daughter was born after three years of marriage, her son six years later.

She was ambitious to improve the social status of her children by educating them. Her daughter, at the age of eight, developed diabetes mellitus, which increased the patient's insecurity and further threatened her ambitions. At this time she was becoming increasingly disappointed, anxious and resentful, and had difficulty in breathing through her nose. This nasal obstruction developed suddenly when several women in her presence condemned a girl for "overstepping conventions." It continued, and grew more and more troublesome, and a year later she had nasal polyps removed.

After another 12 months (November, 1945) her son became ill with abdominal complaints and the subject feared that he, too, might have diabetes. At this time she developed attacks of wheezing during the night. These increased in frequency until she soon was having persistent respiratory distress with an accompanying dry cough.

She came for study during a symptomless period, practically free of wheezing. Her nasal mucous membranes were examined and found to be moderately pale (40 on the color scale). The turbinates were flat (1 + swollen) and the airways open. For several minutes a discussion ensued of her daughter's diabetes, and of why she had married her husband. Another examination of her nose was made. The subject began to wheeze. Her nasal mucosa was now redder (60 on the color scale) but the turbinates showed no more swelling and there was, as yet, no obstruction nor increase in secretion. During the intravenous injection of 0.25 gram sodium amytal, she became relaxed, smiled, and her wheezing disappeared. She was then asked questions about her former fiancé, and she talked about having thrown away opportunities for marital happiness, economic security, productive offspring and favor with her family. She complained that she had lost her figure and had become obese and had relatively little to look to in the future. Wheezing and coughing became severe.

At this point her nasal mucous membranes were bright red (70–80 on the color scale), wet, turgid, swollen (3+) with hyper-secretion and there was almost complete obstruction to breathing through both nares.

She was again interviewed during a period of mild status asthmaticus. In the hypnoidal state induced by 0.5 gram sodium amytal, five minutes following the intravenous injection she was lying comfortably without respiratory distress or wheezing, nor were abnormal sounds heard when her chest was auscultated. A conversation was started. When she spoke of her father she began to wheeze and complain that she could no longer breathe comfortably through her nose. She said he was kind, but that he "pushed" her ahead in school and would let her have no "pleasures." She talked about her husband's inadequacies in learning and earning, and of her disappointment in her children. "I hoped they wouldn't be wild like they are and would grow up to be nice people." Her wheezing was so severe that she had to sit up and had difficulty in talking. Her nose was completely obstructed. At this point she was urged to elaborate a fantasy about going to a dance with a group of gay friends, and a second time the wheezing stopped for five minutes. But, when the suitor, who had thought her "too young," was discussed, she became tense and sober and the wheezing was again almost as marked as it had been before. Once more the patient was diverted by jovial remarks. She relaxed and was free of wheezing and nasal obstruction, 45 minutes after the beginning of the observation.

In short, when faced with assault or threat, the activities of this woman were such as to involve herself more deeply in her difficulties rather than to free herself by taking action. Her general behavior through the years had, so to speak, been one of "cutting off her nose to spite her face."

Against local intrusion, this protective response, which is characterized by shutting out the noxious agents and neutralizing their effects by dilution and washing away, may prove highly effective. But, against situational threats involving interpersonal relations, the nasal and other airway changes in this patient afforded incomplete relief and were often productive of discomfort.

Such morbid developments seemed to be relevant to illness in a large proportion of a series of patients carefully studied who had chronic or recurrent nasal disease and "sinusitis." For example, in one individual observed daily during eight months, nasal hyperfunction which accompanied a period of serious frustration and conflict resulted in pain under the zygoma and headache together with hyperalgesia and redness, clinical features often noted with sinusitis." Antral empyema was not demonstrated, although even slight stimulation of the engorged and extremely sensitive nasal structures reproduced or intensified the pain.

Also, the diaphragm may participate in such a defense reaction. For example, in certain persons during periods of threat the dome may flatten and the excursion diminish due to sustained contraction of the muscular sheet. The patient then complains of difficulties in getting "a full breath," and tight "cramp" sensations in the substernal region. The muscles about the chest and neck may also exhibit sustained contraction, thus further increasing the difficulty in ventilatory exchange.

There appears to be some broad biological significance to this reaction of

shutting out and washing away at the head end of the organism. During weeping, the nose, as well as the eyes, participates in this reaction; furthermore, in some individuals, deeper structures including the bronchi and the diaphragm constrict during threatening situations, thus participating in the reaction of exclusion.

Respiration consists of an in-and-out circulation of air through the respiratory passages. Shutting out thus involves equally a shutting in. In effect, the organism diminishes its exchange with its environment. An individual limits the extent of his participation in the situation about him. Thus insulated, he takes in less and gives out less. "Shutting out" then becomes part of an overall reaction of non-participation and its "shutting in" aspect may include the repression of resentments and conflicts.

The "shutting out-shutting in" pattern, especially when maintained for long periods, is evident in the personality features and social behavior. As in all individuals expressing conflict between divergent purposes, the character develops distinct facets, some expressing drives which are unacceptable in terms of the individual's standards. The subject may be unaware or incompletely aware of his conflicting aims.

As a result of the conflict of forces in this unstable equilibrium the overt behavior of the subject may be that of quiet bravery and hard work, or of "smiling through tears," progressing to frank whimpering and clinging, or any combination or alternation of the conflicting elements. The content of the behavior appears to be: "Everything is 'just fine,' but look at my plight! Lend me support. Is it right that I be exposed to such trouble? Can't something be done about it? It isn't my fault. Don't you, too, abandon me."

Subjects exhibiting the "shutting out-shutting in" pattern are essentially defensive and "close mouthed," talk with difficulty about relevant personal matters and seldom take steps to improve their state. Yet aggression may be evident in the pursuit of a beloved object or desperate clinging to that which lends security. A lively show of love and affection is a basic requirement and is readily accepted. In many who are deprived of devotion and tenderness in early life, events which threaten such emotional support in later life induce exacerbations of the defensive reaction.

If the individual's insecurity mounts, and threats, therefore, become more hazardous, ultimately the dual program may no longer be maintained. The patient then presents a picture of sad and petulant protest, crying for help and struggling for breath.

*Protective Patterns of Defense: (b) Involving the esophagus as well as the bronchi.* Faulkner has reported other examples of the "shutting out or non-participation reaction" in the esophagus and bronchi of subjects during examination with an esophagoscope or a bronchoscope. Thus a man, aged 75, complained of being unable to swallow solid food and of having difficulty at times in swallowing liquids. These dysphagic symptoms had developed

suddenly three weeks previously when he had been informed that he was to be denied continuance of his $40.00 a month "old age pension" from the State. Relief authorities had discovered that he had savings in excess of the amount which entitled him to State assistance.

Faulkner observed in this man contraction of t'.e entire length of the esophagus. When the patient was asked to imagine how it would feel to be put back on the pension roll again, the walls of the esophagus relaxed and the lumen opened. Faulkner then bronchoscoped his patient to ascertain whether or not similar narrowing would be found involving the tracheobronchial tree, and if so, whether this would also respond to suggested threats, or assurance. He observed that the lumen of the right main bronchus was reduced in size to one-third its usual diameter. There was definite limitation of movement of the walls of both the bronchus and the carina or bifurcation. The customary luminal widening on inspiration and narrowing on expiration were absent. When asked to recall how he felt when the candidate he favored won the recent Congressional election, the lumen of the bronchus immediately widened appreciably and showed the usual inspiratory widening and expiratory narrowing.

Discussion had revealed that his Congressman's victory was associated with the hope that his pension would be continued. When asked how he would have felt had his Congressman lost, the bronchial lumen immediately narrowed again until it was one-third of its original size. Furthermore, when asked how he would feel if he were to be promptly restored to the old age pension list and assured that he would positively remain on it for the balance of his life without further investigation, the bronchus opened widely, breathing became deep and normal and inspiratory and expiratory bronchial movement began again. But at the suggestion that he might never again receive his pension, and at his age be forced to find employment when so many were already unemployed, the lumen again narrowed, the bronchial walls quivered and breathing became short, labored and rapid. Faulkner subsequently confirmed these findings on a series of patients.

It therefore appears from these observations that the respiratory, alimentary, orbital and other skeletal muscle patterns of the head and elaborate verbal, interpersonal and social patterns may act as a unit of function or separately in shutting out an environment that is literally or symbolically noxious.

*Protective Patterns of Offense:* (*a*) *Involving cardiovascular and ventilatory functions.* Such shutting-out, non-participation patterns stand in contrast to those described by Cannon, who observed short-lived changes in the hostile cat confronting the barking dog. Under these circumstances, there occurs a diminution of salivary secretion, and circulation. Digestive activities stop and food may remain for hours in the digestive canal without being acted upon. The heart beats faster, the blood pressure is increased and there is redistribution of blood in the body with less in the organs of

digestion and more in the muscles. The cat is in an optimal state for fight or flight, ready to be the attacker or the attacked, the pursuer or the pursued. The struggle which follows may determine life or death. Under these circumstances the great muscles of the limbs and trunk may be used in strenuous and prolonged effort. Digestion is of secondary importance if life is at stake. In addition, great effort is associated with a large increase in the amount of air that is breathed into the lungs and out again, and the widening of the bronchioles and shrinkage of the nasal structures facilitate the total movements of air.

Thus, all these apparently disconnected changes, including those in the respiratory passages, become a part of a single process. They are directed towards making the total organism more effective in the struggle. It is clear, moreover, that in such an urgency the element of inner conflict is minimal.

However, in man, the mobilization pattern may be as readily associated with conflict as other bodily patterns. Indeed, among subjects with essential hypertension, strong conflict with repression of hostility has been recognized as a characteristic feature. It is evident that the biologic pattern is one for action. The following instances illustrate such an action pattern in relation to symptoms.

A 50-year old Jewish male "cloak and suit" worker had had hypertension from time to time during 10 years. He complained of lightheadedness on exertion and headache, substernal pressure and painful precordial sensations not related to exercise. His symptoms followed a recent upper respiratory infection. The examination, on hospital admission, revealed a blood pressure of 210 mm. Hg systolic and 120 mm. diastolic, and a slightly enlarged heart. His electrocardiogram showed depression of $ST_{1 \text{ and } 2}$, low amplitude of $T_{1 \text{ and } 2}$ and slight left axis deviation. The patient was interviewed while on the ballistocardiograph bed, and respiratory, pulse, blood pressure, and cardiac output measurements made. The resting level of blood pressure was 175 mm. Hg systolic and 100 mm. diastolic. The interview revealed that the subject had an uncompromising, demanding wife who imposed her relatives upon the patient in his business; she "cared" little about his personal well being. She complained when the patient felt obliged to visit his aged mother; but when the patient acquiesced to her demands and remained at home, she went out to visit her friends and left the patient alone. During this narration, the subject at first sobbed and then became angry and poured out instances of his wife's iniquities. He complained that the "aggravation" aroused by the discussion was characteristic of what he experienced much of the time, especially when at work or at home. Specifically he noted choking sensations, substernal pressure without radiation and occasional giddiness. The blood pressure was elevated from 175/100 to 220/130 and cardiac output rose 40 per cent during the interview. The patient complained of precordial sensations. The cardiogram changed slightly but definitely with elevation of the ST segments and of the T waves (which Master considers a positive test for coronary insufficiency). The functions did not return to resting levels at the end of the interview and reassurance was not effectively produced. Respiratory tracings showed shallow rapid respirations identical before and after the interview. The same electrocardiographic changes and symptoms subsequently were produced by the effort involved in the Two Step test.

A second example of a reaction pattern involving cardiovascular and respiratory function is as follows:

A 34-year old woman complained of attacks of nocturnal dyspnea. She had essential hypertension with no evidence of irreversible vascular disease. She was interviewed while lying on the ballistocardiograph bed. Records of respiration, pulse, blood pressure, and cardiac output were taken before, at intervals during and after the interview. She was told to talk freely and not hesitate to display her feelings. Her statements were recorded and chronologically related to the physiological observations. The interview itself represented a stress-producing situation. During the interview the patient was aware of and complained of feelings of isolation and loneliness because of her husband's absence. (He was in the Army and overseas.) She described working for a perfectionistic employer under work conditions which all recognized as difficult and which made "perfect work" impossible. Nevertheless, her employer, during his tension states, loudly disapproved of the patient's performance; and the latter, herself a perfectionist, was deeply hurt and enraged. During her married life and before her husband's departure she was able at the end of the working day to voice her anger and regain her personal dignity through her husband's sympathy and support. But after his departure and because of her stand-off, aloof manner, which precluded confidential discussion with friends, her suppressed anger turned to rage and her tension mounted. At the time of the interview she was aware only of tension, but told about obsessive and morbid fears. The fear of poisoning from the gas jet of her refrigerator caused her to turn it off at night. More lately she had feared that she might hurt someone or herself. She also had murderous dreams.

During the interview with this patient, the blood pressure was elevated from 125/90 to 185/120 and the cardiac output was elevated 20 per cent over the resting level. They returned to resting levels after reassurance and a hopeful formulation. Respiratory tracings done before and after the interview demonstrated that as a result of the interview the minute ventilation doubled and the utilization coefficient halved, without significant alteration in the oxgen consumption.

The effects in this patient on blood pressure, cardiac output and respiration were as great or greater and more prolonged during recall of disturbing life situations than following exercise, which was tolerated well. The patient complained of awakening at night with a sensation of constriction in the throat, palpitation and shortness of breath. These symptoms stemmed from an increased stroke volume and increased respiratory ventilation. The patient did not have paroxysmal nocturnal dyspnea associated with failure of the myocardium, but she nonetheless was shown to have under circumstances of stress increased minute ventilation, increased stroke volume and increased cardiac output. After three days in the hospital not "on bed rest" her blood pressure fell from 180/120 to 130/90. The removal of the patient from her threatening environment was probably a major factor in this change. The ventilatory response to the assaults of her situation was the cause of dyspnea in this patient. The dyspnea was a matter of over-ventilation rather than being related to increased need for oxygen.

*Protective Patterns of Offense: (b) Involving the pressor reaction and renal vascular function.* It would appear that many of those who in early life exhibit transient though significant pressor reactions to assault or threat gradually raised the basic level of their systemic arterial blood pressure. Thus a significant proportion of men who exhibited a transient rise in blood pressure from average levels during an initial army physical examination, subsequently developed sustained hypertension. It is obvious that many variables operate in determining whether any inborn protective pattern will assume clinical importance. But it is conceivable that the sustained state of threat in which certain of these persons lived caused inconsequential events to assume special importance, resulting in their remaining in a state of almost continuous readiness for action. The mechanisms implicated in an essential hypertension are unknown, but in one way or another, the kidney is usually involved and therefore consideration of renal blood flow becomes of interest.

It has been demonstrated that renal hemodynamics and excretory functions are relatively stable in any one individual under basal conditions, but may be modified by various chemical agents and procedures. Indeed, profound modifications of renal blood flow were noted by Homer Smith during two disturbing incidents in persons with average levels of blood pressure; in one, a rumor concerning his possible unanticipated and unwanted discharge from the hospital reached the subject; and in the other, a misunderstanding arose concerning the significance of the clearance procedure. Both subjects seemed frightened. The effects were as great as those of a moderate amount of epinephrine. Together with a rise of blood pressure, there was a considerable decrease in effective renal plasma flow and a lesser change in glomerular filtration rate. In our laboratory it was demonstrated in persons with average blood pressure, that similar changes in renal blood flow accompanied both noxious stimulation of the head, and pain induced by cold.

The pathogenesis of the disturbance in essential hypertension is still undetermined. One group of workers showed that in animals, interference with renal blood flow under certain conditions results in chronic hypertension that has many of the features of essential hypertension in humans, but whose precise relationship to human hypertension has not yet been clarified. Another group has done experiments in dogs which indicate that vasoconstriction within the kidney induced by faradic stimulation of renal arteries results in significant reduction in renal function together with rise in systemic arterial blood pressure.

That changes in renal blood flow may be pertinent to the subject with essential hypertension is indicated by the fact that the blood flow in his kidney is small in terms of functioning kidney tubular mass, that is to say, the hypertensive kidney is relatively ischemic as compared to the normal. Also, the degree of depression of renal blood flow parallels approximately the duration and severity of the hypertension. The order in which events

proceed is indicated by the fact that the glomerular filtration rate in early hypertension is entirely within normal limits, but with advanced hypertension and reduction in the number of functioning glomeruli, the glomerular filtration rate is also gradually depressed. In all instances the ratio of renal blood flow to tubular mass is low, indicating a relative ischemia of the hypertensive kidney. As the hypertension advances, the tubular mass decreases but always in such a manner that the renal blood flow is poor in terms of the existing tubular mass. These facts suggest that a defective renal blood flow precedes the onset of faulty excretory function. If kidney ischemia be at all relevant to the occurrence of arterial hypertension, renal blood flow studies in those with widespread vascular reaction to threats become of interest. But before pursuing this topic further, pertinent aspects of the personality of such subjects should be appraised.

Thirty-five subjects with essential hypertension, selected on the basis of their willingness to coöperate, were studied. In essence, insofar as these patients were concerned, the subject with essential hypertension presents a personality which is the resultant of divergent drives. His appearance, movements, manner of speech and interpersonal behavior bespeak one who, when confronted by a threat, or by a dilemma, takes action. He is a tense man, poised and "calm," one who has all the reins in his fingers, but who finds that the task requires constant alertness and readiness to spring into offense.

However, he is prevented from acting offensively and he appears gentle, generous, outgoing, sweet mannered and with much and hearty laughter. When, through repeated threats, the underlying hostility is barely repressed and near the surface, sternness, austerity, ineffectiveness, thinking difficulties, irascibility and grim determination, sometimes featured by mirthless laughter, dominate. Then the state of the individual becomes so precarious that threats or noxious stimuli which would be considered relatively minor, such as plunging the hand into cold water, call forth a major pressor response. At such times the patient may present easily recognized features of his anxiety. During "Amytal" hypnoidal states, he may describe feeling as though "something is hanging over my head." Ultimately he may become tense, agitated or depressed.

In view of these facets of the character and personality, it became of interest to investigate renal hemodynamics in subjects with essential hypertension during rise in blood pressure initiated by threats in the form of discussion of topics known to have a significant relationship to the personality structure.

Situations or threats that jeopardized the security based on the subject's need of approval or love from members of the family, or from authority, were, to those studied by us, especially disturbing. Exceedingly important in several men was the fear of being disapproved by the mother. Indeed, symbols that aroused this basic conflict produced visible evidence of tension, with accompanying pressor reactions of considerable magnitude.

In 18 of these hypertensives without evidence of renal disease, or abnormality of renal function by the usual clinical tests, renal blood flow and glomerular filtration rate were ascertained by the now well known para-amino-hippuric acid method. The first procedure carried out after the arrival of the patient was catheterization with a No. 16 Foley soft rubber catheter in order to permit him to become used to the sensation and allow about an hour and a half for him to reach a basal state. Sodium para-amino-hippuric acid was used for the estimation of effective renal plasma flow and inulin for glomerular filtration rate. Clearance for successive periods of 15 and 20 minutes were measured over about two hours. The first two or three clearance periods were utilized for controls during which the patient was reassured and every effort made to prevent sensitive topics from being brought up. Then, during the next one or two periods of 20 or 15 minutes each, topics of known importance were abruptly introduced, usually having to do with interpersonal relations between the patient and members of the family. Following this, the discussion was turned to neutral topics and an attempt made to engender feelings of security in the patient, during which time several additional clearances were determined. Blood pressures were measured at frequent intervals. At various points during the procedure some of the patients received sodium amytal. The following protocol is representative.

A 41-year old married Jewess had been found to have an elevated blood pressure a year and a half ago. She complained of a frequent dull ache on top of her head and a sensation "like a tight hat" around her head. Outwardly she presented a show of "calm" and a bland attitude and claimed she led a "really happy life." But doing her housework, she said, "got her excited" and left her feeling exhausted.

In the hospital, she was observed during an interview, and her blood pressures recorded at intervals. At first she appeared tense, and was anxious concerning the procedure of the interview (B.P. 188/104, dropping to 148/88 while talking of pleasant, neutral topics). When abruptly asked, "How are things at home?" blood pressure rose to 180/88. She indicated strong dependent needs for love and praise from her husband and described him as considerate and thoughtful (B.P. 198/108). She told of her greatest emotional crisis occurring when she received a telegram which she was reluctant to open lest it tell of her husband's death. "I screamed and yelled" (B.P. 196/100). "I felt considerable relief when I found it contained news of the death of my mother" (who had given her little affection and whom she hated). She became tearful in expressing resentment against her mother "for the way she treated my father" (B.P. 196/100). Again, when she spoke of her father as being "gentle and kind," her blood pressure was 186/106.

During the interview and pressor response, the renal blood flow decreased approximately 25 per cent and peripheral resistance in the kidney increased 40 per cent. The patient was then urged to relax, and was given an intravenous injection of 0.25 mg. of sodium amytal. Blood pressure fell rapidly to 140/88 and remained there for the next 15 minutes, though renal blood flow continued to remain at a lower level than before the injection of Amytal.

Later she was interviewed during an hypnoidal state following intravenous administration of 0.3 gm. Sodium Amytal. Before the injection, blood pressure was 255/125. In the hypnoidal state she became well relaxed and began to talk freely.

Blood pressure fell to 170/110. When she told of receiving the telegram she mentioned above, blood pressure became 195/130. There was a fall to 180/120 when she spoke of taking life realistically. She next mentioned her hatred for her mother and discussed her father's death. Blood pressure rose to 230/150. When she began to joke with the physicians there was a precipitous fall to 170/120.

This woman, with essential hypertension, presented a reaction to threats featured by hostility and resentment, and an attempt to deal with threats by action. However, there was an associated prominent need to placate, to maintain peace at any price. Therefore hostility was repressed and action directed elsewhere than at the real danger. This misdirection led to incomplete resolution of the problem and further frustration.

Rises in diastolic and systolic blood pressure were similarly induced in 17 other persons with essential hypertension by discussion of topics of personal significance, usually having to do with family interpersonal relations, without, at the same time, inducing outward evidence of strong emotional reaction. The rise in blood pressure under such circumstances was accompanied by renal vasoconstriction which was either proportional to that of the body as a whole or more intense than necessary to compensate for the rise, reflected by decreases in renal plasma flow of 17 per cent to 25 per cent of control level. In some patients renal vasoconstriction outlasted the rise in systemic blood pressure. This became conspicuous when the degree of peripheral resistance in the kidney vascular apparatus was appraised, and represented an increase in resistance of as much as 40 per cent. The increase of renal vasoconstriction was located principally in efferent glomerular arterioles although both efferent and afferent arteriolar constriction occurred. Fall in blood pressure during induced feelings of security was accompanied by vasodilation of the efferent and afferent arterioles.

From these and other facts, it may be inferred that the kidney in persons with arterial hypertension exhibits an abnormal vascular pattern, characterized by increased arteriolar tone, and the latter may be further increased by threats or assaults that evoke protective reactions of a pressor nature.

However, it may not be inferred that the experimentally induced renal vasoconstriction is the cause of the observed hypertension. Thus, preliminary observations have revealed that patients with arterial hypertension exhibit a pressor response during experimentally induced stress both before and after thoracolumbar sympathectomy (T7–L3), although the renal vasoconstriction elicited before is no longer demonstrable after sympathectomy. It is apparent from these observations that the blood pressure may still rise in response to threats, even though the kidney does not participate in the vascular reaction. Secondly, it was possible to demonstrate in those with and without arterial hypertension that the renal blood flow is not increased as the result of renal denervation by sympathectomy, but remains unchanged or may actually be decreased. In one non-hypertensive subject with a unilateral kidney denervation (sympathectomy) equal blood flow in both organs was observed. The meaning of these observations on the relation of

adrenergic impulses and kidney blood flow to arterial hypertension in well established hypertensives is not clear. Certainly, as far as can be demonstrated in the latter, renal vasoconstriction due to sympathetic impulses is not the essential defect in the mechanism of hypertension. Nonetheless, there remains the probability that neurogenic factors are pertinent to the beginnings of the hypertensive syndrome. It is suggested that as part of the protective reaction early in the life of the potential hypertensive, adrenergic impulses induce neurohumoral effects involving the adrenal cortex and the kidney which ultimately result in irreversible kidney ischemia and arterial hypertension.

Furthermore it is suggested that such renal vasoconstriction may, if prolonged, damage the renal blood vessels and the parenchyma, and lead secondarily to further elevation of blood pressure. The cost of the reaction to the heart and to the vascular apparatus of such organs as the brain and kidney may ultimately be great enough to destroy the organism.

*Inappropriate Use of Protective Patterns.* Nasal obstruction, though effective in keeping out dust and irritant gases, is less effective against blows or unrequited love. As mentioned above, closing the air passages and increasing the mucous membrane secretions minimize the damaging effects of a gas or of an irritant particle, but such devices do not protect against a thorn in the foot or make less destructive the hostility of a parent or marital partner. Indeed, they often lead to additional distress. The closure of the esophagus protects the stomach from a corrosive agent but does not protect the child from neglect by its parents or resolve the resentment of a rejected husband. In short, the shutting-out and washing-away pattern is another of those ancient protective devices which have specifically beneficial effects under certain and limited circumstances. It fails under others just as the total reaction pattern described by Cannon fails to serve the stockbroker watching a ticker tape that may spell disaster. Thus, the human organism in reaction to threats uses devices which may be inappropriate, but the setting in motion of an integrated pattern of reaction devised to deal with threats appears to afford a measure of relief from anxiety and tension.

*Mixing of Protective Patterns.* The various biologic patterns involved in protective response to assaults or threats fall, as mentioned above, into offensive and defensive categories. A single individual usually operates in one or another frame, but he is likely from time to time to vary his methods, alternately using defensive and offensive patterns and occasionally sustaining both types of effort simultaneously. Such behavior may reflect the state of conflict of the individual as to how to deal with a threat, whether to take action against it or exclude it. The patterns may appear divergent, but are not in opposition in the broadest sense, both being aimed at protection of the organism.

It is in this light that the coexistence, for example, of gastric hyperfunctioning (with or without lesions) and nasal obstruction can be viewed. The nasal obstruction implies an attempt on the part of the organism to shut

out, rather than to deal with the situation. Gastric hyperfunctioning, on the other hand, implies readiness for action.

The result of conducting two campaigns at the same time is a costly expenditure of energy. This duality of method is further illustrated in the trembling, fidgeting and tapping of the feet, coupled with sustained muscular contraction which probably represent the incomplete resolution of a drive to move away from the site of the dangerous situation, opposed by a stronger drive compelling the individual to remain in place to face whatever befalls him. It would appear that once a bodily pattern of reaction to some threat has been set in motion, however inadequate may be its protection, the anxiety and other uneasy feelings which accompanied it initially may become secondary, thus to remain for indefinite periods.

Some of the reactions to threats are accompanied by bodily changes that are called to the attention and may be the basis for complaint (nose, stomach); of other reactions the individual may not be aware until long after the pattern has been established, and irreversible tissue damage has resulted.

*Stock Factors, Organ Selection and Inferiority.* Dominant protective reaction patterns are apparently deeply ingrained since they occur in many individuals of the same stock under analogous conditions. It seems likely that they are stockbound, analogous to the retriever pattern in dogs, running pattern in the horse, hoarding in squirrels, building and space orientation in birds and insects, and sham death in the opossum. The implication is that the individual and his clan meet life in a particular way, and to a degree, in a different way from the members of other stocks. A given protective pattern may during long periods of relative security remain inconspicuous, and then, during stress, become evident as a disorder involving respectively the gut, the heart and vascular systems, the naso-respiratory apparatus, the skin and general metabolism.

When one asks why one organ rather than another is involved during stress, there is no satisfactory answer. More profitable is the question of how the organ is implicated in a biologic pattern of offense or defense.

The repeated or prolonged participation of a given organ in a protective pattern is not evidence of the weakness or inferiority of that organ even though because of such participation it fails to maintain its structural integrity. True, involvement of the part may indicate that the individual is weak or living under undue stress, but the organ can hardly be said to be weak, and indeed may be especially developed and strong.

*Destructive Results of Protective Patterns.* For the most part, protective devices are designed for short term use and as such fall well within the physiologic budget of the organism. Thus, transitory changes in nasal function indicative of being on guard, like the transitory elevations of blood pressure and gastric function which may similarly follow threats, are well tolerated. The difficulty arises when the threatened individual sustains emergency patterns as "the way of life." The time necessary for the occur-

rence of structural changes in some tissues may be hours, whereas in other instances long periods would seem to be required. Furthermore, the protective pattern once established often creates fresh disturbances in and about the organism, increasing its vulnerability so that new threats perpetuate the need for protection; therefore, disturbances may persist long after the initial threat ceases to apply. For example, compulsive individuals who need to "outdo" others find that their behavior creates new foes, which requires perpetuation of the protective pattern. Also, it has been shown elsewhere that during gastric hyperfunction, as a part of the protective pattern, when highly acid gastric juice comes in contact with an unprotected eroded surface, a vicious cycle is created in which further stimulation to hyperfunction occurs.

Again, as elsewhere in the body's ducts and cavities, the establishment of obstruction within the nasal cavities often leads to secondary infection. Minor anatomical deformities such as spurs or deviations of the nasal septum may assume significance when the already narrowed airways become occluded by swelling of the turbinates consequent upon some threatening life situation. Once it has taken root an infective process can prolong the period of morbid changes in the nose and lead to serious disease and incapacity long after the precipitating emotional conflict has been resolved.

Serious incapacity on the part of the patient may also occur when only minor structural changes are present. As noted in earlier studies on headache, many patients over-react to minor disturbances or sensations when that site takes on special meaning with regard to the integrity of the individual. For instance, past conditioning experiences may endow the nose with special significance and cause minor disturbances in nasal function to have ominous implications for the individual.

As the processes of defense and offense may lead to disastrous results in the airways, stomach, heart, blood vessels and kidneys, so may the repression of emotions associated with these patterns prove destructive to the whole individual.

The formulation here presented illuminates certain well defined reaction patterns. It is evident, however, that some reaction patterns accompanying life experiences are not clarified by this concept. For instance, there are widespread bodily changes and symptoms that occur in some individuals during the period immediately following stress or emergency. Thus headache, vasomotor changes, vomiting, diarrhea and other gastrointestinal dysfunction, changes in amount of tissue fluids, dejection, fatigue, prostration may be absent during the period of duress, only to occur shortly after. Also, there are bodily changes which seem to represent the purposive or quasi-purposive attempts at some immediate or obvious gain, as exemplified by the man who develops a reversible palsy in one arm when called upon to enter battle. Although such adjustments may conceivably be protective in nature, or sequelae of protective reactions, it may be more profitable to see them as implying the existence of other, as yet ill-defined, adaptive mechanisms.

## Epitome

Interference with or threat to his life or love, or blocking the proper fulfillment of an individual's potential, causes him to react as though to assault. He responds defensively or offensively, or both, depending on his nature, his past experience, and the situation. Under these circumstances he struggles to regain what has been lost and to rid himself of interference, in order to fulfill his drives. Such struggles evoke what may be called emergency or crisis protective patterns.

A considerable part of the human equipment has to do with meeting emergencies and dealing with crises. Protective reactions are set off by threats usually in the form of symbols, which have been connected with danger in the past.

Some of these reactions represent widespread mobilizations to provide extra fuel and energy for vital parts of the organism. Others appear to be focused on regional defenses, notably at portals of entry and exit. Offensive and defensive, general and local protective devices may operate together and separately.

Along with these conspicuous bodily preparations go certain feelings and attitudes which, stemming from the same needs, have the same goals.

The organism sacrifices at such times some functions or capacities for the sake of promoting others that are most important to meet the adverse situation. Although there is a degree of specialization in the sense that one or another protective arrangement is dominant, discrimination is not exact. In a threatened man it is common to find a variety of protective reactions, some of which are extremely pertinent, others less so, and still others minimally effective.

Because his drives are primitive and even violent, they may be out of keeping with a man's conception of himself and therefore unacceptable. Thus, the drive denied or not fully recognized by the subject, the subsequently evoked protective reaction patterns may unwittingly become sustained. A few of these reaction patterns have been intensively studied.

During assaults or threats arousing conflict with anger and a pattern of offense, the stomach prepares itself for eating with increased blood flow, acid secretion and motility. The gastric mucosa may become turgescent and the blood vessels friable. With forceful gastric contractions, bleeding readily ensues and erosions of the mucous membrane may follow.

Conspicuous among defensive protective reactions are those involving the nose and airways. It has been observed that in reaction to assault, certain individuals occlude their air passages and limit the ventilatory exchange by vasodilatation, turgescence, hypersecretion and smooth and skeletal muscle contractions. The changes, especially in the upper respiratory airways, give rise to a variety of symptoms, notably pain and obstruction, the latter often leading to secondary infection, and the prolongation of morbid processes.

Also, a non-participation behavior pattern and attitude is exhibited in interpersonal relations.

Offensive protective reactions involving chiefly the cardiovascular and renal systems were exhibited in certain aggressive individuals. These persons, in reaction to assault, mobilized their equipment, causing the work of the heart to be greatly increased through increased rate, output and peripheral resistance. Especially notable in those with pressor reactions and essential hypertension was a significant reduction in renal blood flow during periods of experimentally induced assault, an effect with potentially ominous implications.

It is suggested that when the individual maintains such emergency measures, symptoms and tissue damage may follow.

In brief, man, feeling threatened, may use for long-term purposes, devices designed for short-term needs. Costly protective activities are essential and life saving. They are devised for fleeting emergencies so that he may destroy those forces that threaten his survival. But, they are not designed to be used as life long patterns, and when so utilized, may damage structures they were devised to protect.

These considerations constitute the basis of a good deal of human suffering and sickness. To prevent these disorders, more knowledge concerning the origin of these patterns in childhood is necessary. To interrupt them once they have become well established requires a vigorous and fresh approach to methods and means. To deal with these disturbances, it is necessary to study the functions of organs widely separated in the body, and because the methods require cutting across the lines which usually separate the various medical skills, the horizon of the physician must be broadened. It follows that interest in these illnesses cannot be limited by delineations of a new specialty. The pursuit of these matters is a prime medical responsibility of our day.

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# EFFECT OF THE ANTIMONY COMPOUNDS, FUADIN AND TARTAR EMETIC, ON THE ELECTROCARDIOGRAM OF MAN; A STUDY OF THE CHANGES ENCOUNTERED IN 141 PATIENTS TREATED FOR SCHISTOSOMIASIS *

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## INTRODUCTION

DURING 1945 there were admitted to Harmon General Hospital 488 patients with proved or suspected *Schistosomiasis japonica* acquired during the campaign on Leyte in the Philippines. These patients have been the subject of an intensive and detailed study.[1]

Because the drugs tartar emetic (antimony potassium tartrate) and fuadin (antimony pyrocatechin disulfonate of sodium) used in the treatment of this disease have been reported to cause serious cardiovascular reactions and even death,[2] frequent electrocardiograms were taken during treatment to determine what changes might be expected. In a significant number of patients the changes in the electrocardiogram were striking and might have been mistaken for evidence of myocardial damage. In no instance did the clinical behavior of the patient warrant such a diagnosis. The changes induced, their reversible nature and significance form the basis of this report. For the guidance of medical officers a preliminary note on the changes observed in the first 66 patients treated has been published.[3]

## LITERATURE

Although tartar emetic and fuadin have been used extensively in the treatment of schistosomiasis in endemic areas, there exists a paucity of references to the effects upon the electrocardiogram of man. In Egypt alone, Khalil [4] in 1936 estimated 1,000,000 courses of antimony treatment a year were given with a mortality of 0.2 per cent. A complete review of the literature up to 1938 [5] contains no reference to the electrocardiographic changes induced by antimony compounds.

In cats changes have been described in the electrocardiogram following the intravenous injection of double salts of antimony.[6]

Mainzer and Krause [2] who were the first to report significant electrocardiographic changes in man following tartar emetic, analyzed in detail the electrocardiograms of 12 Egyptian patients infected with *Schistosoma hematobium, Schistosoma mansoni,* or both. They were treated with a course

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of tartar emetic. The authors considered the electrocardiograms pathological in three of their cases, unaltered in three others and showing minor changes in the remainder. Most of the alterations were described in the T-waves and ST segments. They believed the extent of the changes was proportional to the bradycardia induced by antimony and regarded the results as an intoxication of the heart muscle, which in exceptional cases, might lead to "heart failure and death, probably through auricular fibrillation."

## Materials and Methods

In 200 of the 488 patients with an overseas diagnosis of *Schistosomiasis japonica,* electrocardiograms were taken shortly after admission to this hospital and from 22 to 162 days after the patients had completed treatment overseas. They had received variable amounts of fuadin, in 6 per cent solution, ranging from 10 to 109 c.c.—with an average dose of 40 c.c. Some had been given tartar emetic in doses comparable to those to be described under plan two below, and a small number had had both fuadin and tartar emetic.

The electrocardiograms were all within normal limits except in four instances. Two showed ventricular premature contractions from single foci. The third had low voltage T-waves in the standard leads with negative T-waves in all precordial leads. The fourth presented a short PR interval with a wide QRS complex (Wolff-Parkinson-White syndrome). Although the ova of *S. japonicum* may lodge in the myocardium and cause inflammatory reactions,[7] no clinical evidence of heart disease due to this condition was found in any of the patients. As a group they ranged from 20 to 40 years and represented an average cross section of previously healthy young soldiers who had been in the Pacific area under field or combat conditions for periods of several months to two years.

On the basis of overseas records and the findings at this hospital the diagnosis was confirmed by finding of ova in the stools in 80 per cent of the patients. In the other 20 per cent the diagnosis was justified on the history of exposure and clinical findings.[1] No patient was started on treatment at Harmon General Hospital unless ova were found in the stool.

The first 141 patients to be treated form the basis of this report. Each patient was observed for 90 days after treatment. If the stools became positive he was again treated and electrocardiograms recorded. Of the group, 35 patients required two courses of treatment and five patients required three courses during the period of observation which began in April and ended in November 1945.

The patients were divided into comparable groups to test the efficacy of fuadin, tartar emetic commercially prepared in ampoules, and tartar emetic freshly prepared. Since the frequency and degree of the changes induced in the electrocardiogram by both types of tartar emetic were the same, the patients who received this medication will be treated as one group.

Four plans of treatment were followed to determine the most effective course of therapy. In view of the importance of the dosage and frequency of injection of these drugs, it is necessary to consider in detail the several treatment plans employed.

*Plan 1.* A group of 33 patients were treated with fuadin given intramuscularly in 6 per cent solution. Each cubic centimeter was equivalent to 0.0087 gm. of antimony. The first three injections were 1.5 c.c., 3.5 c.c. and 5 c.c. on consecutive days. All subsequent injections were 5 c.c. given on alternate days until a total of 65 c.c. had been given in 25 days. Of this group, 25 patients required a second course of 65 c.c. of fuadin within 40 to 90 days. Following the second course at least five patients again showed the ova in their stools 30 to 60 days later. These were treated with tartar emetic, 416 c.c., as in plan four.

*Plan 2.* A group of 67 patients received tartar emetic intravenously in 0.5 per cent solution. Each cubic centimeter was equivalent to 0.0018 gm. of antimony. The first four injections were 8 c.c., 12 c.c., 16 c.c., and 20 c.c., given very slowly on alternate days. The fifth and all subsequent injections were 24 c.c. given in the same way for a total of 320 c.c. in 29 days. Of this group 10 patients required a second course of 320 c.c. of tartar emetic within 60 to 90 days.

*Plan 3.* A group of 15 patients received 105 c.c. of fuadin in a manner similar to plan one for 41 days.

*Plan 4.* A group of 31 patients received 416 c.c. of tartar emetic in 0.5 per cent solution as in plan two for 39 days. In this group are included five patients who had failed of cure in their second course of treatment with 65 c.c. of fuadin.*

Every patient had at least one electrocardiogram prior to treatment. This served as a control from which all subsequent changes were noted. There was also an electrocardiogram 30 to 60 days after completion of treatment, to determine the time of return to normal. This tracing served as an additional check on the normal when a second course of treatment was necessary.

Early in the study the electrocardiograms were taken on an amplifier tube type of apparatus (General Electric) and on the hospital model string instrument (Cambridge). It was soon evident that comparison of tracings taken on these two machines was difficult and inclined to be inaccurate due

* The following table gives the conversion values of c.c. of fuadin or tartar emetic to gm. of antimony as employed in this study.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fuadin | c.c. | 10 | 20 | 45 | 50 | 65 | 80 | 105 |
| | gm. | .087 | .174 | .392 | .435 | .566 | .696 | .913 |
| Tartar Emetic | c.c. | 20 | 80 | 128 | 176 | 248 | 320 | 416 |
| | gm. | .036 | .144 | .230 | .317 | .446 | .576 | .743 |

to variations in the height of the complexes, despite adequate standardization. All records subsequently were taken on the string instrument.

All tracings were taken under standard conditions, usually one hour after injections, with the patient lying in a comfortable prone position. The precordial lead was $CF_4$. In several instances in which abnormal findings were recorded in this lead, additional leads—$CF_1$, $CF_2$, $CF_3$, and $CF_5$—were taken.

Because of the uncertainty of the time of appearance of changes in the electrocardiogram during treatment with the two drugs, frequent records were taken in the early phases of the study, including tracings immediately and one hour after injection, in the case of tartar emetic.

Patients receiving 65 c.c. of fuadin had records taken after 5 c.c., 45 c.c., and 65 c.c. of medication. Later in the study, the electrocardiogram after the 5 c.c. dose was discontinued. Patients receiving 105 c.c. of fuadin had tracings recorded after 50 c.c., 80 c.c., and 105 c.c.

In the tartar emetic group, electrocardiograms were taken after 80 c.c., 248 c.c. and 320 c.c. of medication. Later this was changed to 176 c.c. or 200 c.c. and 320 c.c. In those receiving 416 c.c., an electrocardiogram was recorded after this dose in addition to the others.

In a few individuals who showed marked changes in the electrocardiogram, special studies were made, including daily records. In all, about 900 electrocardiograms were read and compared by one observer. Each tracing was analyzed for rate, PR interval, alterations in form and height of P, QRS and T-waves. In representative groups detailed measurements of QRS width and QT intervals were tabulated in the serial records.

## Findings

The alterations in the electrocardiograms were, for the most part, confined to the T-waves. To simplify description and analysis, the changes in the T-waves have been classified from one to four plus based upon the following criteria (figures 1 to 4):

1. One plus change was equivalent to a decrease of 30 to 50 per cent in the T-wave voltage in two or more leads.

2. Two plus change represented a further decrease in T-wave voltage with a lengthening of the proximal slope and a rounding of the summit of the waves in two or more leads.

3. Three plus change was a continued decrease in the height of the T-waves to extremely low voltage or isoelectric levels in three or more leads, accompanied by a slight negativity of the terminal portion in one or more of the leads. The summits of the waves presented no sharp angles, but were rounded or flattened.

4. Four plus change represented an alteration from positive T-waves to sharply negative or even cove plane T-waves in three or more leads, with low voltage in the remaining lead.

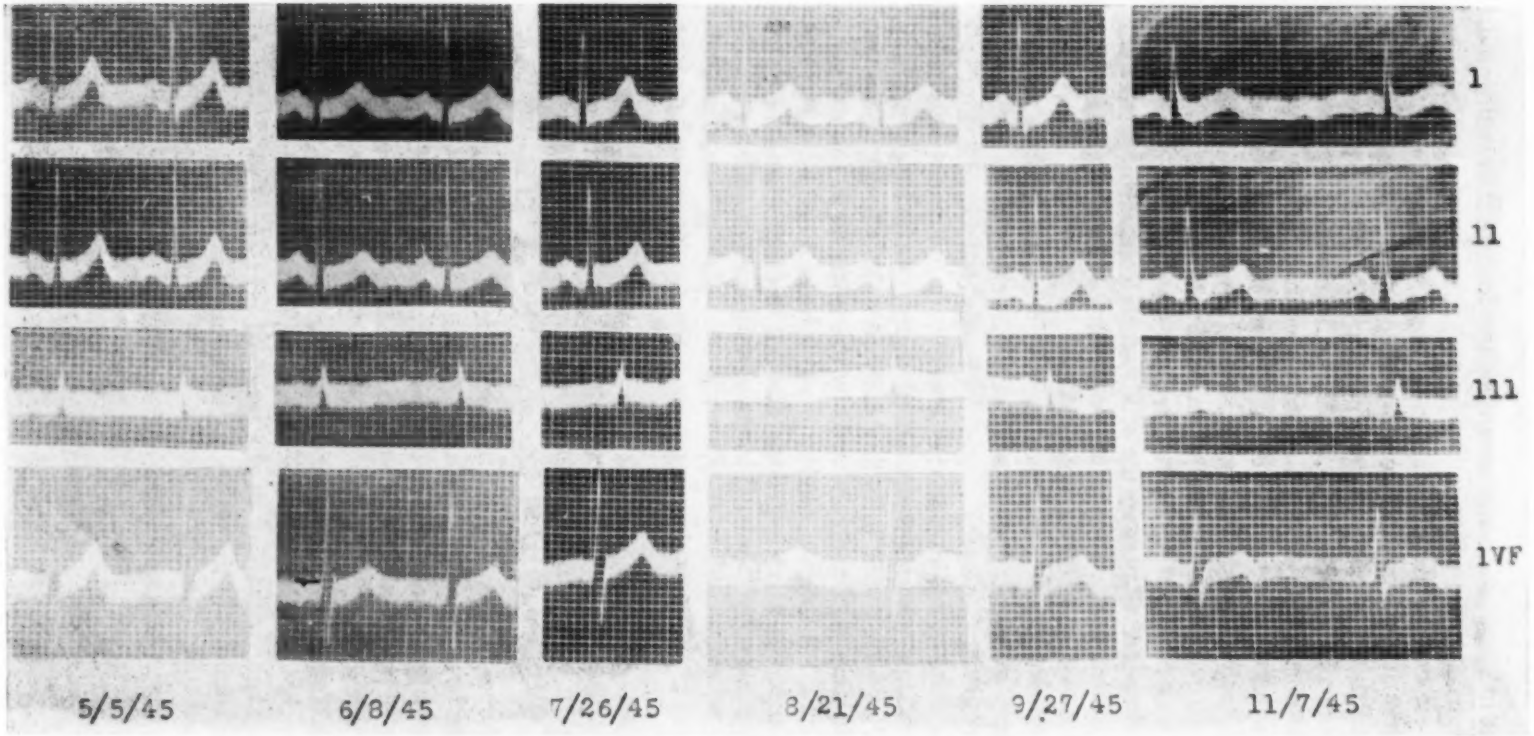


FIG. 1. R. C. 23 year old male with schistosomiasis. One plus change in T-waves produced during treatment with two successive courses of 65 c.c. of fuadin in 6 per cent solution (equivalent to .566 gm. antimony in each course) and one course of 416 c.c. of tartar emetic in .5 per cent solution (equivalent to .743 gm. antimony).

5/5/45—Control record 94 days after treatment with 40 c.c. of fuadin overseas.
6/8/45—One plus change after first course of 65 c.c. of fuadin.
7/26/45—Return to control level 48 days after treatment.
8/21/45—One plus change after second course of 65 c.c. of fuadin.
9/27/45—Return to control level 37 days after treatment.
11/7/45—One plus change after 416 c.c. of tartar emetic.

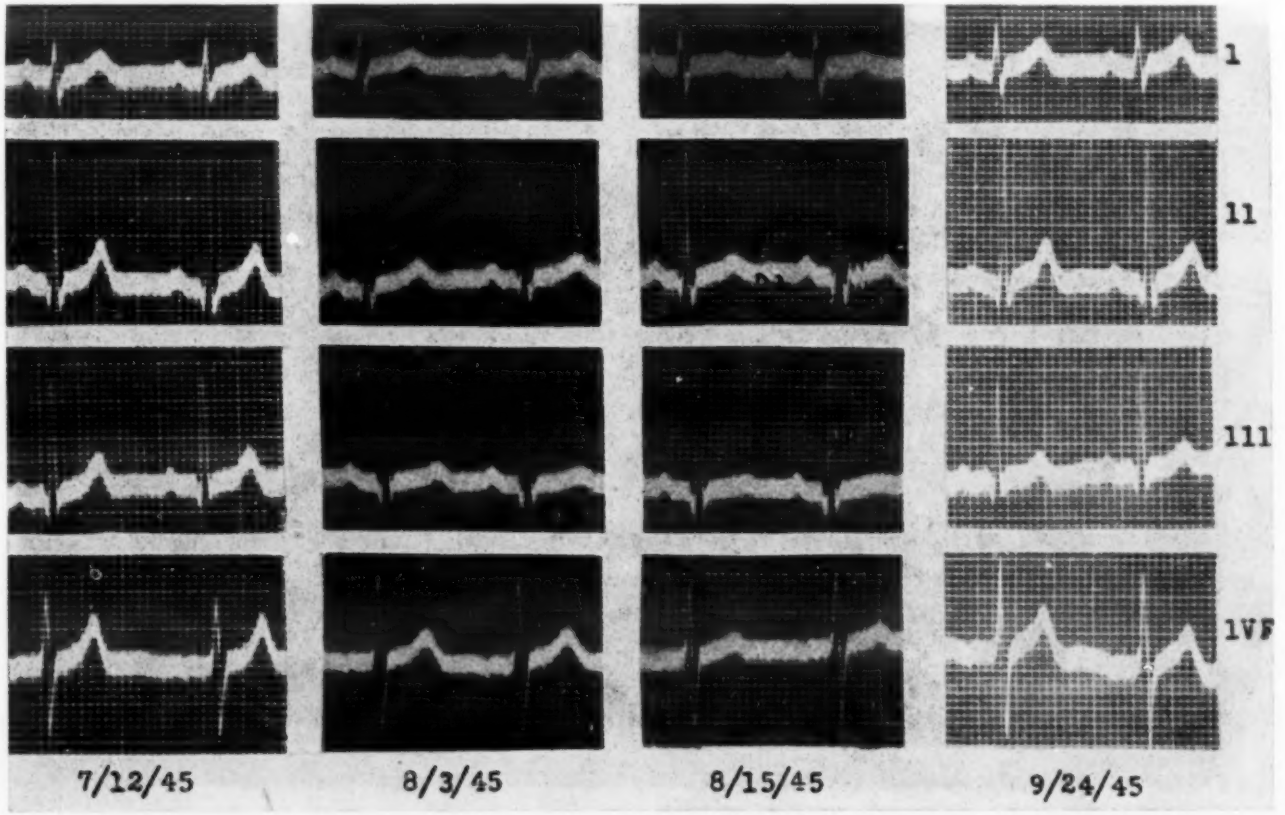


FIG. 2. P. B. 21 year old male with schistosomiasis. Two plus changes in T-waves produced during treatment with 320 c.c. of .5 per cent solution of tartar emetic (equivalent to .576 gm. of antimony).

7/12/45—Control record 121 days after treatment with 40 c.c. of fuadin (.348 gm. antimony) overseas.
8/3/45—One plus change after 176 c.c. of tartar emetic.
8/15/45—Two plus change after 320 c.c. of tartar emetic.
9/24/45—Return to control level 40 days after treatment.

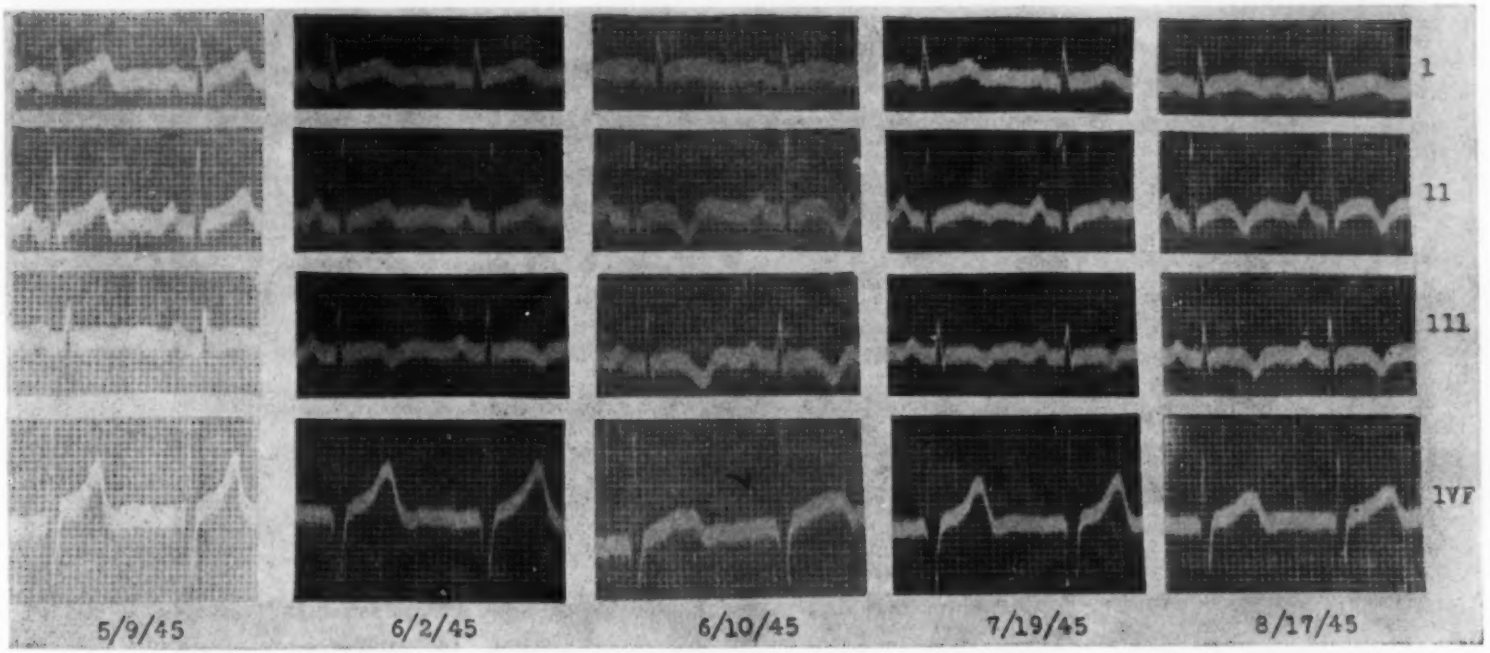


FIG. 3. W. K. 29 year old male with schistosomiasis. Three plus change in T-waves produced during treatment with two successive courses of 65 c.c. of fuadin in 6 per cent solution (equivalent to .566 gm. antimony) followed by (figure 3 A) four plus changes during a course of 416 c.c. of tartar emetic in .5 per cent solution (equivalent to .743 gm. antimony).

5/9/45—Control record 32 days after treatment with 40 c.c. of fuadin overseas.
6/2/45—Two plus effect after 45 c.c. of fuadin.
6/10/45—Three plus effect after 65 c.c. of fuadin.
7/19/45—Two plus change still present 39 days after treatment.
8/17/45—Three plus change after second course of 65 c.c. fuadin.

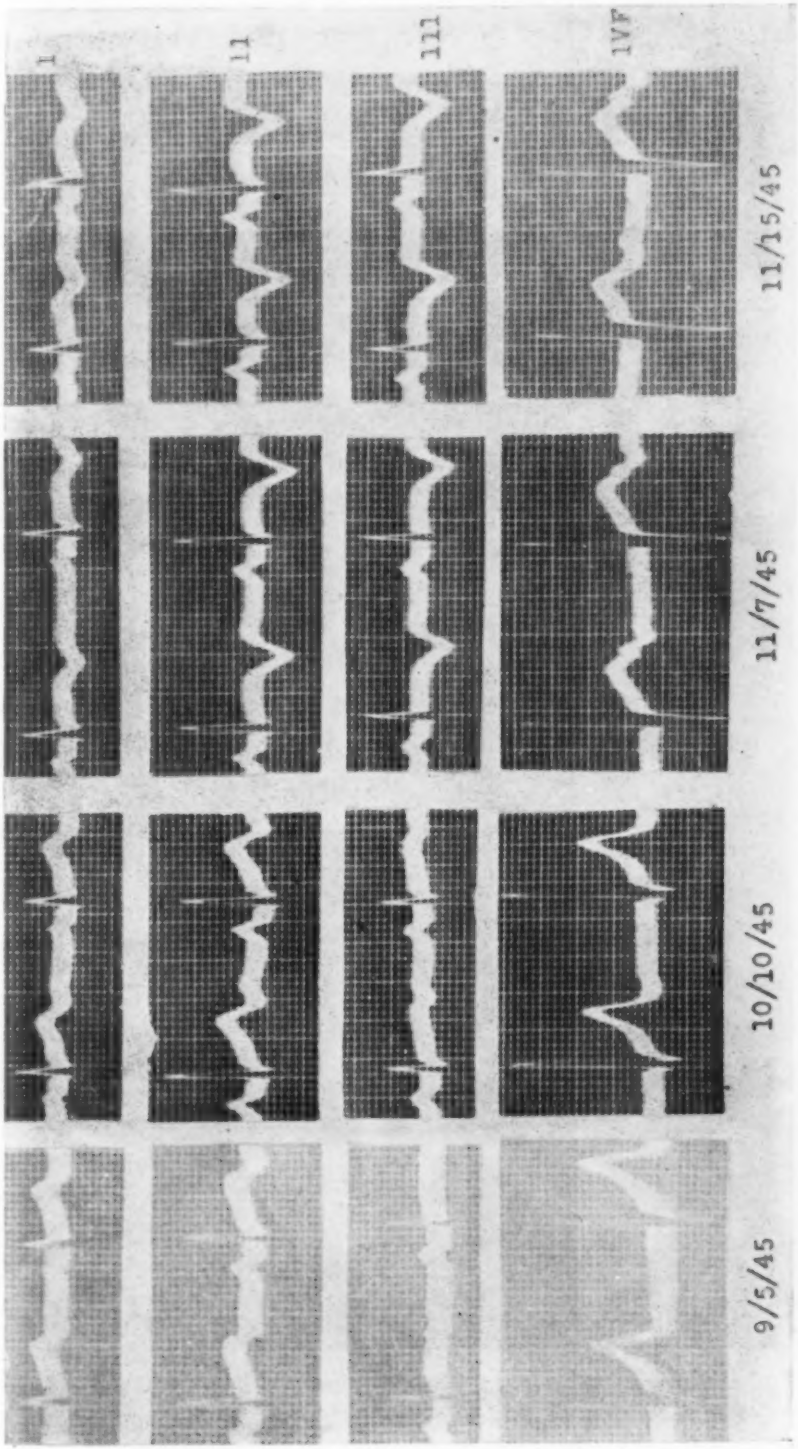


FIG. 3 A. Same patient as in figure 3.
9/5/45—One plus effect still present 19 days after second course of treatment.
10/10/45—Return to control level 54 days after second course of fuadin.
11/7/45—Four plus effect after 320 c.c. of tartar emetic.
11/15/45—Four plus effect unchanged after 416 c.c. of tartar emetic.

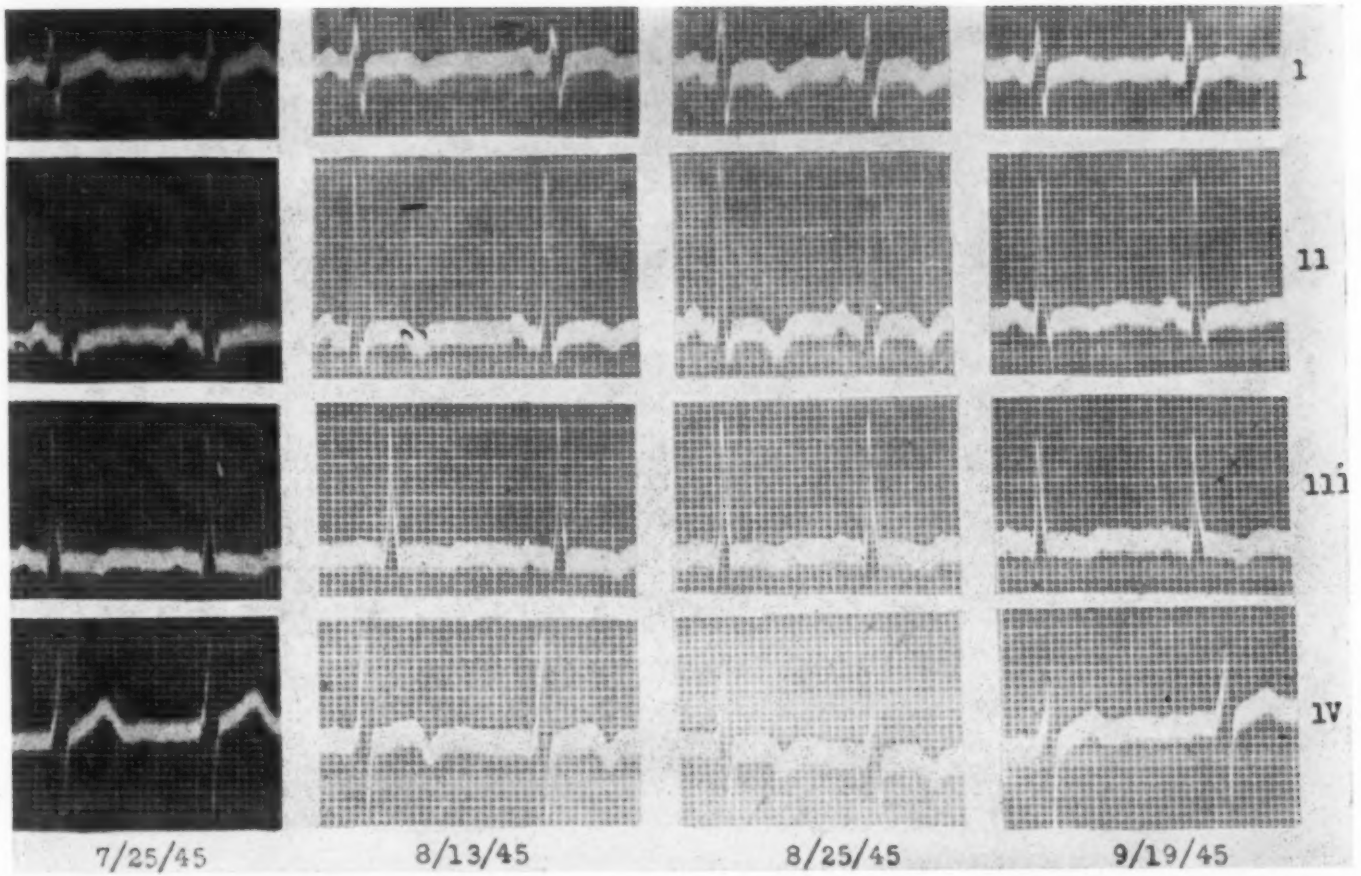


FIG. 4. B. K. 23 year old male with schistosomiasis. Four plus change in T-waves produced during treatment with 320 c.c. of tartar emetic in .5 per cent solution (equivalent to .576 gm. antimony).

7/25/45—Control record 162 days after treatment with 320 c.c. tartar emetic overseas.
8/13/45—Four plus effect after 176 c.c. of tartar emetic.
8/25/45—Four plus change more pronounced after 320 c.c. of tartar emetic.
9/19/45—Two plus change still present 25 days after treatment.

About 5 per cent of the records were difficult to classify in the above groups. They were considered with the group showing the lesser changes. When the control tracing showed a negative or diphasic T-wave, usually in Lead III, the change under medication was a further decrease in negativity. In the one patient previously mentioned whose control tracings showed low voltage T-waves in the standard leads and negative T-waves in all precordial leads, the alteration under tartar emetic was graded one plus and consisted of a slight negativity of T-waves in Leads I, II, III and a further increase in the depth of $T_4$. No definite heart disease could be established clinically in this patient.

In one patient who was treated with 416 c.c. of tartar emetic, as in plan four, all precordial T-waves developed a marked rounding of their summits and a widening of their bases without change in the height of the waves. The QT interval increased from .36 to .56 second with a decrease in rate from 68 to 62 per minute. The P-waves in Leads II and III were also altered (figure 5).

TABLE I

Frequency of Lead Involvement

| Leads Involved | Tartar Emetic | Fuadin | Total | |
|---|---|---|---|---|
| | | | Number | Per Cent |
| I, II, III, IV | 57 | 18 | 75 | 56 |
| I, II, IV | 26 | 11 | 37 | 28 |
| I, II, III | 13 | 4 | 17 | 13 |
| I, II | 1 | 1 | 2 | 1.5 |
| II, IV | 1 | 0 | 1 | .7 |
| II, III, IV | 0 | 1 | 1 | .7 |
| Total | 98 | 35 | 133 | |

Table 1 indicates the frequency with which the different leads were affected and the combinations of leads involved in 133 patients. When changes in the T-wave occurred following administration of either fuadin or tartar emetic, 56 per cent of the tracings showed all four leads affected, 42 per cent showed three leads and 2 per cent showed only two leads.

Although in 98 per cent of the electrocardiograms showing changes, three or four leads were involved, the degree of alteration in each lead was not always the same. This is illustrated by those tracings in which the T-waves changed from positive to negative. Table 2 indicates the frequency pattern with which negative T-waves appeared in the different leads in records showing three to four plus changes. These tracings were obtained during 39 courses of treatment in 34 patients. The incidence of negative or diphasic T-waves in the control records is included. The most frequent combination occurred as a negative $T_2$ and $T_3$. Lead III seemed to be the most sensitive to this type of change when the T-wave in only one lead became negative.

9/19/45—Two plus change still present 25 days after treatment.

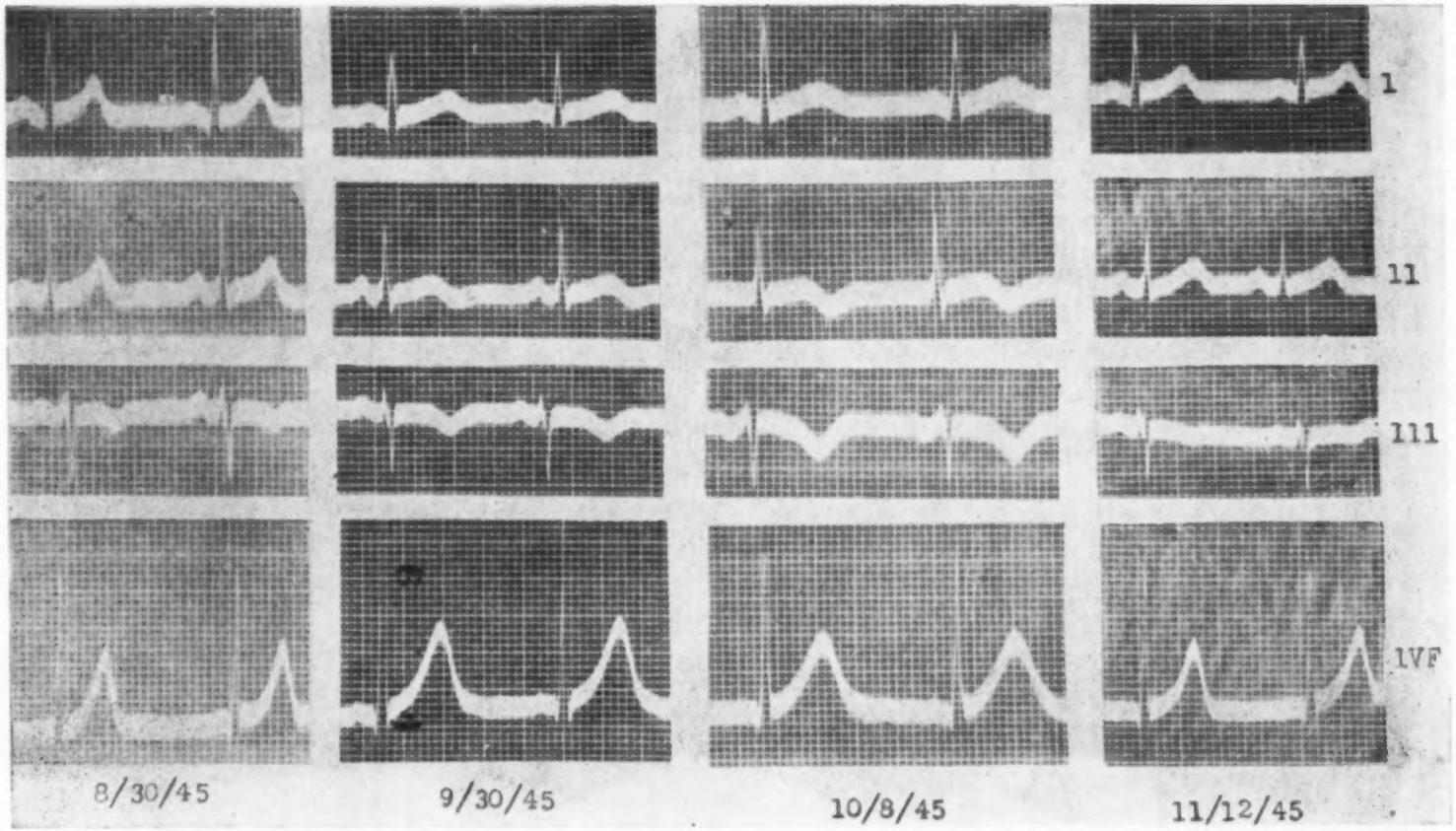


FIG. 5. J. H. 23 year old male with schistosomiasis. Three plus change in T-waves after 416 c.c. of .5 per cent solution of tartar emetic (equivalent to .743 gm. antimony). Unusually wide T-waves in precordial leads. QT interval prolonged.

8/30/45—Control record 120 days after treatment with 80 c.c. of fuadin overseas.
9/30/45—Two plus effect after 320 c.c. of tartar emetic.
10/8/45—Three plus effect after 416 c.c. of tartar emetic.
11/12/45—Slight change, one plus, still present 35 days after treatment.

TABLE II

Frequency of Negative T-Waves in Electrocardiograms Showing Three and Four Plus Changes during Treatment

| Combination of Leads Involved | Frequency of Combination | Frequency of Negative or Diphasic $T_3$ in Control ECG |
|---|---|---|
| II, III | 13 | 7 |
| I, II, III, IV | 6 | 5 |
| III | 6 | 0 |
| II, III, IV | 5 | 2 |
| III, IV | 4 | 1 |
| I, IV | 2 | 0 |
| I, II, III | 2 | 0 |
| I, II | 1 | 0 |

Elevation or depression of the RT or ST segment was not encountered in any of the groups. The proximal slope of the T-wave might change to become a long gradual slope or the wave flatten out completely, but it always arose from the base line. When the wave became negative and assumed a cove shape, the point of origin was still the isoelectric line, without elevation or depression of the point of origin.

Superficially, the negative T-waves resembled a coronary T-wave, but their origin and the slightly positive slope before the negative terminal portion helped to differentiate them. In some instances the terminal portion would become negative while the proximal portion was still quite rounded and several millimeters high. In succeeding tracings, following further medication, the height of the wave decreased and the terminal portion became more sharply negative and angular. A group of six patients was followed with frequent electrocardiograms, not more than a few days apart, after completion of treatment. The return of the T-waves to normal was in the reverse sequence of their production. They became less negative, slightly rounded and higher, and finally positive with sharp summits.

The T-wave changes in groups one and two plus were not striking and might have been considered within normal limits had no control tracings been available. In groups three and four plus the electrocardiograms were definitely abnormal and without cognizance of the effect of the medication could have been interpreted as showing evidence of myocardial damage.

Table 3 shows the frequency of changes encountered under the different plans of treatment. Every patient receiving a course of tartar emetic showed an alteration in his electrocardiogram. In 30 per cent of the patients these changes were in groups three and four plus and would be considered definitely abnormal. Only 6 to 14 per cent of the fuadin treated patients showed such marked changes.

When the treatment was repeated, the degree of electrocardiographic change was not significantly different in the second course of fuadin. Those showing no change or one plus remained the same. Four patients who previously showed no alteration now had one plus effect. In the five patients who were given 416 c.c. of tartar emetic, after two courses of 65 c.c. of fuadin, the patients all showed some degree of change. Table 4 shows

TABLE III

Distribution of the Degree of Change in the Electrocardiogram After a Course of Fuadin or Tartar Emetic

| Drug | Total Antimony Grams | Total Cases | No Change | | One Plus | | Two Plus | | Three Plus | | Four Plus | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | No. | % | No. | % | No. | % |
| Fuadin 65 c.c. | .566 | 33 | 14 | 43 | 13 | 39 | 4 | 12 | 2 | 6 | 0 | — |
| Fuadin 105 c.c. | .913 | 15 | 3 | 20 | 7 | 46 | 3 | 20 | 1 | 7 | 1 | 7 |
| Tartar Emetic 320 c.c. | .576 | 67 | 0 | — | 27 | 40 | 20 | 30 | 16 | 24 | 4 | 6 |
| Tartar Emetic 416 c.c. | .743 | 31 | 0 | — | 5 | 16 | 16 | 52 | 7 | 22 | 3 | 10 |

the degree of alteration in the electrocardiogram in two successive courses of treatment in 25 patients, and in three courses of treatment in five patients of the same group.

TABLE IV

Comparison of Degree of Change in the Electrocardiogram in Successive Courses of Treatment in 25 Patients

| Case Number | First Course Fuadin 65 c.c. | Second Course Fuadin 65 c.c. | Third Course Tartar Emetic 416 c.c. |
|---|---|---|---|
| 1 | + | + | + |
| 2 | + | + | + |
| 3 | + | + | ++ |
| 4 | 0 | + | ++ |
| 5 | +++ | +++ | ++++ |
| 6 | ++ | ++ | |
| 7 | ++ | ++ | |
| 8 | ++ | + | |
| 9 | +++ | ++ | |
| 10 | + | + | |
| 11 | + | + | |
| 12 | + | + | |
| 13 | + | + | |
| 14 | + | + | |
| 15 | + | + | |
| 16 | + | + | |
| 17 | 0 | + | |
| 18 | 0 | + | |
| 19 | 0 | + | |
| 20 | 0 | 0 | |
| 21 | 0 | 0 | |
| 22 | 0 | 0 | |
| 23 | 0 | 0 | |
| 24 | 0 | 0 | |
| 25 | 0 | 0 | |

In 10 of the 67 patients who were treatment failures with 320 c.c. of tartar emetic, and who received a second course 30 to 60 days later, the degree of change in the individual patient was practically the same. Those who, in their first course showed minimal changes of one and two plus, continued to do so, and those who showed three or four plus remained the same.

Although the quantitative change in the electrocardiogram in the tartar emetic and fuadin groups was different, qualitatively the alterations encountered were identical. This is well demonstrated in a group of five patients who were treatment failures after the second course of 65 c.c. of fuadin. They were treated in their third course with tartar emetic 416 c.c. The degree of change with tartar emetic was slightly greater than with fuadin, but the alterations in the T-waves, as they developed under tartar emetic, were indistinguishable from those produced by fuadin (figures 1, 3, 3 A).

The amounts of medication required to produce alterations in the electrocardiogram have been analyzed for all four plans of treatment. From table 3 it is evident that within each treatment group the same amount of total medication induced a variable response in the electrocardiogram in different individuals. One plus alterations occurred with as little as 10 c.c. of fuadin, in three patients. As the medication was continued, two of these patients developed two plus changes after a total of 45 c.c. of fuadin. The electrocardiogram of the third patient showed no further change, even after 65 c.c. of fuadin. The average dose required to produce one plus change was about 45 c.c. and the largest dose was 105 c.c. The smallest dose necessary to induce a two plus effect was 45 c.c. and ranged up to 105 c.c. of fuadin. A three plus change occurred with as little as 50 c.c. and the same individual gave a four plus with 80 c.c. It was the only maximum effect seen with fuadin.

In the tartar emetic group the earliest changes were noted in several patients with as little as 20 c.c. Most patients required 80 c.c. to produce a one plus effect. The smallest dose necessary for a two plus change was 80 c.c. and ranged up to 416 c.c. One patient who exhibited a one plus change with 20 c.c., showed three plus with 80 c.c. and four plus with 128 c.c. It usually required from 176 c.c. to 416 c.c. of tartar emetic to induce a three plus change. Four plus alterations were seen with 176 c.c., 200 c.c., 320 c.c., and 416 c.c. in four different patients.

In addition to T-wave changes, other alterations of minor nature were noted. In two instances infrequent ventricular premature beats and in one instance A–V nodal beats developed during treatment with tartar emetic. Although these alterations may not be an effect of the medication, they were not present in the control tracings and disappeared after treatment. No other disturbance in rhythm was detected.

The heart rates in our patients as recorded in their electrocardiograms during treatment revealed no pronounced bradycardia. In three instances the rate was 56 to 58, compared to control values of 60 to 75 per minute.

Although the literature [5, 9] accepts as a pharmacologic fact that antimony slows the heart rate, it was not a striking or constant phenomenon in our patients. The records in 181 courses of treatment were analyzed for changes in rate. In 56 courses there was no significant change after treatment. In 48, there was an increase in rate from six to 30 beats with an average of 10 to 15 beats per minute. In 77, there was a decrease in heart rate from six to 30 beats with an average of 10 to 15 beats per minute. There was no relationship of the T-wave changes to the alterations in the heart rate during treatment.

The P-waves were practically unchanged in the serial tracings. In four instances, two of which are mentioned in the text, $P_2$ and $P_3$ became isoelectric or negative.

The PR interval showed no constant or significant alterations during treatment. No value above .20 second was encountered. Minor prolongations from .16 to .18 or .20 second were seen in about 15 per cent of the patients, but its significance is doubtful.

Alterations in the shape and height of the QRS complex were conspicuously absent under all plans of treatment. It was remarkable that this portion of the electrocardiogram remained unchanged despite striking alterations in the T-waves.

The QT interval was measured and compared with the rate to determine any prolongation or shortening during treatment. The standard used was derived from the formula $QT = 0.39 \sqrt{RR} \pm .04$ where RR represents the time interval between beats (8). The curves of this equation form a convenient method of plotting the changes. About 20 per cent of the tracings showed a slight to moderate prolongation of the QT interval. In all instances in which the prolongation occurred, it was due to the widening of the base of the T-wave and not the QRS complex. In two patients under treatment with fuadin, a prolongation was seen in tracings in which the T-waves were not altered sufficiently to meet a minimum or one plus change.*

The reversible nature of the changes became apparent in the follow-up tracings after treatment. In six patients electrocardiograms were taken every few days after the course of fuadin of tartar emetic was completed. It was of interest to note that records taken several days later might show more change than those on the last day of therapy. The beginning of the return to normal could be detected as early as one week after treatment. In those showing only one plus changes there were several whose tracings, 10 to 14 days after treatment, were the same as their control. The majority of patients were not reëxamined until they had returned from a furlough or leave, 30 or more days after a course of treatment. In 90 per cent of those receiving the short course of fuadin or tartar emetic the electrocardiogram was normal by the time the patient returned from furlough, 30 to 60 days later. The mean furlough time was 35 days. The remaining 10 per cent

* Several records were encountered in which the QT interval of the control was longer than the normal limits. The change in these patients was a slight further prolongation under treatment.

at this time showed slight T-wave changes that were only significant when compared with the control and did not exceed those seen in our one plus group. It is worth noting that even in patients treated with the larger doses of fuadin or tartar emetic, the tracings in all but 10 per cent had returned to normal in 60 days.

In one patient who was treated with 65 c.c. of fuadin without any change in the electrocardiogram, an unusual alteration was present on his return from furlough 38 days later. The electrocardiogram showed negative T-waves in all leads equal to four plus changes. $P_2$ and $P_3$ were negative. The following day the P-waves were normal without any change in the T-waves. Within five days the T-waves showed definite indications of returning to the normal pattern. At the end of 38 days, or 76 days after treatment, they were equal to the control except for slight rounding and lowering of $T_2$. This patient did not require a second course of treatment and afforded no opportunity to check this behavior of his electrocardiogram.*

In seven patients who showed T-wave changes of varying degree during treatment, electrocardiograms were taken 30 minutes after 1 mg. of atropine sulfate subcutaneously. The rate increased but there was no effect on the T-waves.

During the course of treatment with tartar emetic, and to a lesser degree with fuadin, the patients develop minor toxic symptoms such as cough, muscle and joint pains, and nausea. The changes in the electrocardiogram showed no relationship to these minor toxic symptoms. Those who exhibited three and four plus alterations had no greater incidence of these complaints than did the patients with one or two plus changes.

## Discussion

Both fuadin and tartar emetic are compounds of trivalent antimony. The toxicity of trivalent antimony preparations is probably related to the liberation of the inorganic antimony from the complex molecule.[9, 10] Although the total antimony in both drugs, as given under treatment plans one and two, was almost equal in amount, the changes induced in the electrocardiogram by tartar emetic were more common and of greater degree. This may be related to the ease with which antimony is liberated from the respective compounds.

In view of the response to trivalent antimony preparations, it was desirable to determine the effect of pentavalent compounds on the electrocardiogram. No references to such studies were found. Leishmaniasis is treated by pentavalent antimony preparations such as neostam and neostibosan. In three American soldiers who contracted the disease in India, treatment at this hospital consisted of an intravenous course of neostam equal to 4.7 gm. in one patient, and neostibosan equal to 5 gm. in the other two. The total amounts of pentavalent antimony injected were equivalent to 1.41

* He was questioned closely concerning the possibility of treatment by antimony medication during his furlough, but denied receiving any. Clinically he was well and had no abnormal cardiovascular findings.

and 2.10 gm. respectively. No effect on the electrocardiogram was noted. A much larger group will have to be evaluated to determine the effect of pentavalent antimony.

Khalil [11] states that individual variations occur in the excretion of antimony. This, he believes, explains the variation in therapeutic response and tolerance. The absorption of fuadin, following intramuscular injection, is very rapid.[9] The excretion begins within 24 hours and may continue for two months or more after a course of treatment.[5] The rate of disappearance of tartar emetic from the bloodstream after injection is probably rapid. In the rabbit it is within 30 minutes.[12] Both tartar emetic and fuadin yield antimony, which is deposited in body tissues. Chemical analysis of tissues taken from a child who died during fuadin therapy indicates that the liver stores a large amount of antimony.[11] In experiments of chronic poisoning of rats and rabbits with tartar emetic over several months, the heart muscle was found to store a proportionate share of antimony.[13]

The selective action of these drugs upon the T-wave, without any significant effect on the other components of the electrocardiogram, leads one to the conclusion that the response noted is due to alterations in the electrical activity of the ventricle. This alteration is probably due to a temporary deposition of antimony in the heart muscle.

The similar changes in the electrocardiogram on repeated courses of fuadin or tartar emetic may be explained by the relative constancy, in any given individual, of the several factors in the body metabolism, which would affect the deposition of antimony. In several of our patients who received repeated courses of fuadin and tartar emetic the changes in the T-waves, in the individual patient, were observed to be identical even in the minor details.

It is possible that variations in deposition and mobilization of antimony, in some patients, may lead to a higher concentration in the heart for several days after treatment is completed. This would explain the behavior of those patients whose electrocardiograms showed greater change several days after treatment than at the time of completion of treatment. The gradual return of the electrocardiogram to normal over a period of 30 to 60 days, following treatment, is in keeping with the known slow excretion of antimony.

The variable dose required to produce the electrocardiographic changes and the lack of additional response in some patients despite continuation of the drug, suggests a balance may have been effected between storage and excretion, to keep the amount in the heart relatively constant. It is not known how much antimony is actually deposited in the heart muscle and what amounts are needed to produce alterations in the electrocardiogram. An average dose of .392 gm. of antimony as fuadin, or .144 gm. of antimony as tartar emetic was required to produce a one plus effect. With such small doses, the amount of antimony stored in the heart must necessarily be still smaller.

The possible relationship of the level of blood antimony to the production of electrocardiographic changes has been considered. From what is known

of the behavior of the group of heavy metals, viz., bismuth, mercury, arsenic, and lead, to which antimony is related, storage in tissues, rather than transient blood level determines the pharmacologic action. The time of appearance and regression of the electrocardiographic alterations is much more in keeping with a storage rather than blood level effect of antimony.*

It may be questioned whether the effects on the electrocardiogram were not due to the whole molecule of fuadin or tartar emetic, or possibly to the potassium ion in the tartar emetic. The similarity of the changes induced by the two drugs speaks for a common origin. Fuadin is a sodium salt of antimony which would suggest that potassium is not a factor. Furthermore, the electrocardiographic changes following potassium intoxication are entirely different. The occurrence of the same qualitative changes in five patients treated with fuadin and tartar emetic successively, again argues for a common denominator of antimony.†

## Summary

1. The trivalent compounds of antimony, fuadin and tartar emetic, employed in the treatment of 141 patients with proved *Schistosomiasis japonica* were found to produce significant changes in the electrocardiogram.

2. These changes were confined to the T-waves and have been quantitatively graded. Records exhibiting the more marked changes, could, without cognizance of the medication, have been interpreted as showing evidence of myocardial damage.

3. In every patient receiving tartar emetic changes were induced in the electrocardiogram. In 57 per cent to 80 per cent of those receiving fuadin, depending on the dosage, similar alterations were found.

4. These changes were of a reversible nature and disappeared within 30 to 60 days after treatment was completed in 90 per cent of the patients. There were no cardiovascular symptoms accompanying them.

5. In repeated courses with the same compound, a similar degree of change was elicited. The alterations produced represent an individual response and are probably associated with the storage of antimony in the heart.

6. The changes induced were of such definite and distinct pattern that in the more marked alteration they may, within the limitations of our present knowledge, be recognized as a specific effect of antimony.

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* In selected patients, blood antimony levels, and the excretion of antimony in urine and stool, have been followed during and after treatment. The results of this work will be reported at a later date. (Unpublished data; Lippincott, S. W., Ellerbrook, L. E., Rhees, M., and Paddock, F. B.)

† No data are available on the effect of sodium antimony tartrate upon the electrocardiogram. Its use in small series would eliminate the question of potassium effects.

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# STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS IN HUMANS

## II. PULMONARY TUBERCULOSIS *

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### Introduction

In a preceding paper,[1] observations on the streptomycin treatment of meningeal and generalized hematogenous tuberculosis were presented. On the basis of these studies and in confirmation of the previous reports of Hinshaw and Feldman,[2, 3] it was concluded that streptomycin is capable of exerting a powerful effect upon the course of tuberculous infections in humans. It was further concluded [1] that in miliary tuberculosis, at least, the development of streptomycin-resistance as detected in vitro, reflects the presence of a drug-resistant infection in vivo.

The present report is concerned with the results observed in 43 patients with pulmonary tuberculosis who received streptomycin on the Cornell-New York Hospital Medical Service during the 19 month period, January 1, 1946 to July 31, 1947. Only those patients, 36 in number, who have been observed for a minimum period of six weeks following the completion of the streptomycin therapy are considered in detail (table 1).

*Outline of the Investigation.* All of the patients were confined to bed during therapy and in the post-treatment period. They were permitted to sit up in bed but were not usually allowed bathroom privileges. No form of collapse therapy was induced in any patient until at least 90 to 120 days had elapsed since the start of antimicrobial therapy.

The type of streptomycin used, the intervals at which the appropriate clinical and roentgenologic examinations were made, and the technics employed in the bacteriologic studies are recorded in a previous communication.[1]

*Streptomycin Regimens.* In the first part of the investigation, all of the patients received 3.0 grams of streptomycin daily, administered intramuscularly in divided

* Portions of this study were presented before the annual meetings of: the American College of Physicians, Chicago, April 29, 1947; the American Society for Clinical Investigation, May 5, 1947; and the Section on Internal Medicine of the American Medical Association, June 12, 1947.

From the Department of Medicine of the New York Hospital-Cornell University Medical College.

The first part of this investigation was conducted under the direction of the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman. The subsequent investigation is a part of the Streptomycin Manufacturers American Trudeau Society program which is being conducted in collaboration with the Tuberculosis Study Section of the National Institute of Health. The streptomycin was furnished by the Chemotherapeutic Committee; by a generous donation from Charles Pfizer and Company, Inc., Brooklyn; and from supplies donated to the American Trudeau Society by the Streptomycin Manufacturers.

The study was aided in part by grants from the National Institute of Health, and from the Lederle Laboratories, Inc., Pearl River, New York.

TABLE I

Classification According to Clinical Type and Presumed Pathological Character of 36 Cases of Pulmonary Tuberculosis. Each Followed for at Least Six Weeks after Completion of Streptomycin Therapy

| Clinical Type (and presumed pathological character) | No. of Cases | Cavity Closure | Sputum Conversion |
|---|---|---|---|
| Group I. *Early Predominantly Exudative*, with recent excavation | | | |
| (a) Patchy pneumonic (with annular, thin-walled cavities) | 11 | 7 | 6 |
| (*b*) Confluent pneumonic (with consolidation but little excavation) | 3 | 2 | 2 |
| (*c*) Progressive primary (with cavitation) | 1 | 1 | 1 |
| (*d*) Caseo-cavernous (with massive caseation and large or multilocular cavities but little evidence of fibrosis) | 3 | 0 | 0 |
| Group II. *Chronic Type*, with fibro-cavernous secondary changes. | 18 | 3 | 5 |
| Total | 36 | 13 | 14 |
| Far advanced | 25 | | |
| Moderately advanced | 11 | | |

doses for a total period of 120 days. The 120 day regimen was selected arbitrarily in an effort to provide antimicrobial therapy for the longest period which was thought to be generally feasible. After 18 patients had been treated, the total period of treatment was shortened to 42 days in an effort to avoid the production of streptomycin-resistant strains of tubercle bacilli.

When preliminary studies of Pfuetze [4] and Hinshaw [5] indicated that the administration of one gram of streptomycin daily in divided doses appeared therapeutically satisfactory and definitely less toxic, the daily dose used in the present study was lowered to one gram administered in a single injection. Only 10 individuals with pulmonary tuberculosis have completed therapy on the one gram-42 regimen and only three among the 36 listed in table 1. It is not possible, therefore, to compare the therapeutic effectiveness of this regimen with the results observed following the use of the three gram daily dose. There is definite evidence, however, that the neurotoxicity of the one gram daily dose is considerably less than is observed with the larger doses. Only one of 10 patients who have completed the one gram–42 day regimen have either subjective or objective evidences of vestibular dysfunction. In contrast, this reaction was observed uniformly in the patients who received the 3.0 gram daily dose for a comparable period.

*Types of Pulmonary Tuberculosis.* A classification of the 36 completed cases, on the basis of clinical type and presumed pathologic character of the disease, is presented in table 1. All cases were of moderately or far advanced extent. One case in a child is listed as of progressive primary type, although the disease differed little from several cases of predominantly lower lobe distribution in adults. All of the patients had progressive lesions and tubercle bacilli were readily demonstrated in the sputum of all. One or more areas of pulmonary excavation were demonstrable in all but two of the cases, both of which were far advanced in extent. In six there were concomitant ulcerative lesions of the larynx or bronchi.

## Observations and Results

*Group I. Early Predominantly Exudative Tuberculosis with Recent Excavation.* Eighteen patients with disease of predominantly exudative character and in whom the greatest part of the pulmonary involvement was known to be recent * were treated. All but one received three grams of streptomycin daily. The results after completion of the antimicrobial therapy in the several types of cases in this group are shown in table 1 (group I).

In general, there was a measurable improvement by recognized criteria during the first six weeks of streptomycin therapy. The degree of change depended to a considerable extent upon the severity of the disease when treatment was started. Thus the amount of subjective and objective improvement was usually much more pronounced in the patients with large areas of confluent pneumonia than in those who had patchy pneumonic lesions with thin-walled cavities. Several in the latter group were afebrile and essentially asymptomatic before institution of the antimicrobial therapy.

Definite clinical improvement of some degree, however, was noted in all patients who had symptoms at the start of therapy. In some instances, the speed with which a striking degree of improvement appeared was comparable to the rapid changes observed in the streptomycin treatment of hematogenous tuberculosis. Defervescence within one week after the start of antimicrobial therapy was observed in seven of the eight patients with exudative lesions whose daily temperatures before treatment had consistently attained 102° F. In addition to the high incidence of temperature defervescence, virtually all of the patients experienced a conspicuous reduction in cough and expectoration and an appreciable gain in weight and in strength.

A change in the character of the physical signs in the chest was frequently noted as early as two weeks after the start of streptomycin therapy. In the confluent pneumonic type (group Ib, table 1) with signs predominantly those of consolidation rather than of cavitation the regression of signs was characterized by reduction in the area over which dullness, bronchial breath sounds and bronchophony were elicited as well as by a striking reduction in the number of râles. The former signs disappeared entirely in one case. In the cases with mixed signs of consolidation and excavation (group Id, table 1) the changes were less conspicuous and a relatively large area of bronchial or amphoric breath sounds persisted. In the type of patchy pneumonic lesion (group Ia, table 1) in which the presence of râles was often the only detectable physical sign, a disappearance or diminution in the number of râles was frequently observed during the first six weeks of streptomycin therapy.

With but a few exceptions, the major part of such clinical improvement as occurred was completed within the first four to six weeks of antimicrobial therapy. Roentgenologically detectable changes also appeared during this

* In all instances less than three months old, by evidence of prior roentgenograms or, as in several of the fulminating types, by history of acute symptomatic onset.

period and continued thereafter as is described below. After the initial improvement, these predominantly exudative cases followed one of several patterns:

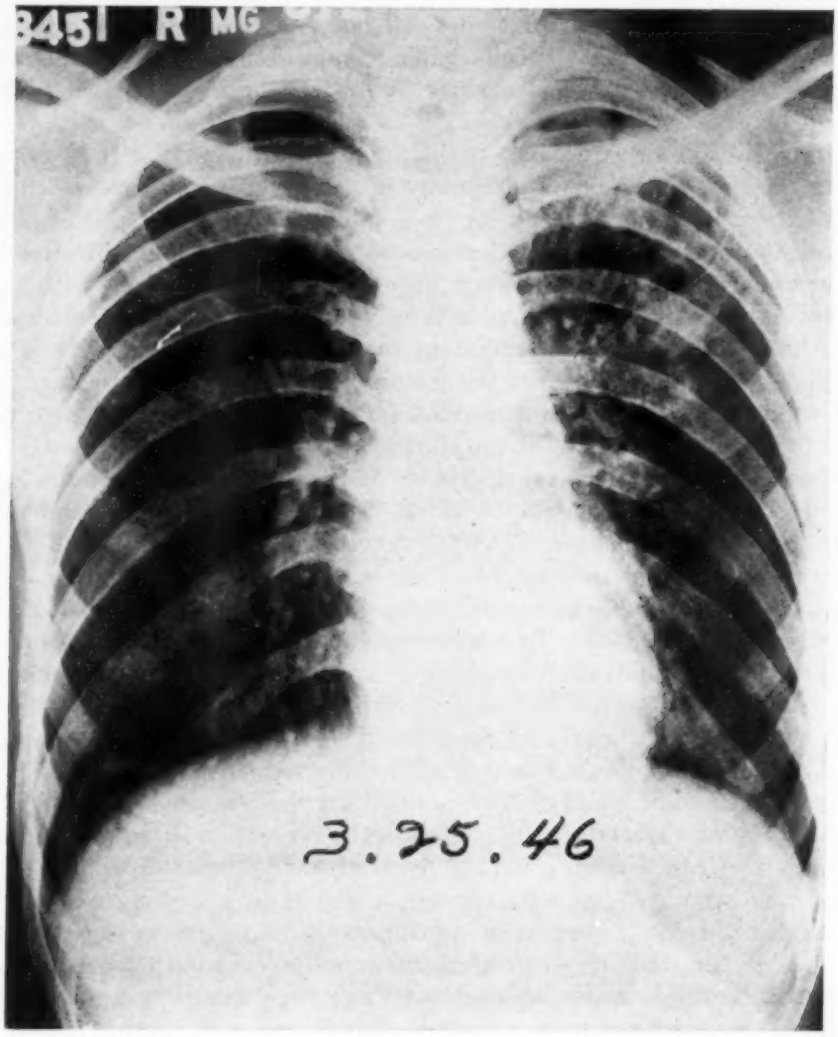


FIG. 1a. Patient C.Ya. Twenty-four year old Chinese man. Symptoms of cough, recurrent small hemoptyses and low grade irregular fever for 2½ months. Roentgen-ray of lungs before streptomycin treatment. Note thin walled cavity in left infraclavicular region and surrounding patchy pneumonic infiltration. Shadows stationary during one month of observation on bed rest before treatment.

(1) Continued quiescence with extensive roentgenologic clearing, cavity closure and sputum conversion. Three of nine such cases, however, relapsed after several months.

(2) Continued quiescence with a variable degree of roentgenologic clearing and cavity reduction but without complete closure or disappearance of bacilli from the sputum.

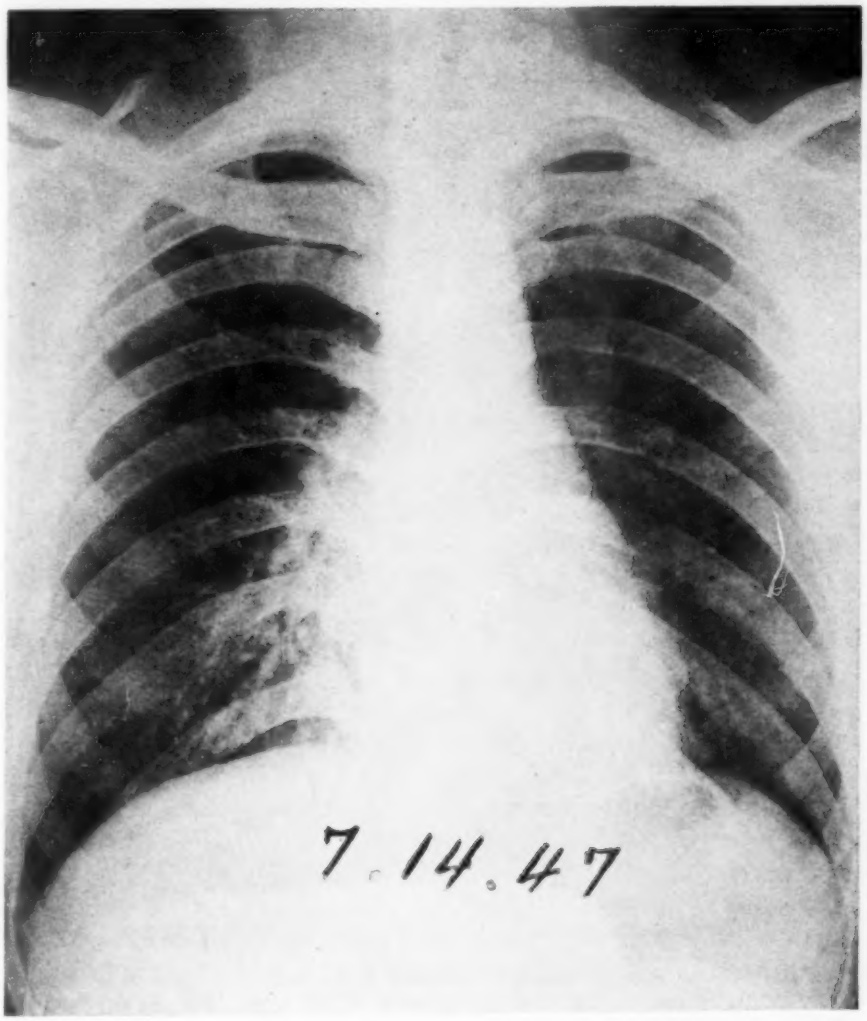


FIG. 1b. Patient C.Ya., 16 months later. Closure of cavity took place within 6 weeks of beginning treatment. Infiltration had regressed extensively within 120 day period of streptomycin administration. Dose 3.0 gm. daily.

(3) A variable degree of symptomatic improvement accompanied by clinical and roentgenologic evidence of continued excavation with resumption of progressive course. The latter phase was usually preceded or accompanied by the appearance of organisms resistant to streptomycin in vitro.

*Continued Quiescence with Cavity Closure (Early Remission).* In nine

of the 18 patients with predominantly exudative lesions, there was extensive clearing of the infiltrative process, with cavity closure * and sputum conversion during streptomycin therapy or in the immediate post-treatment period.

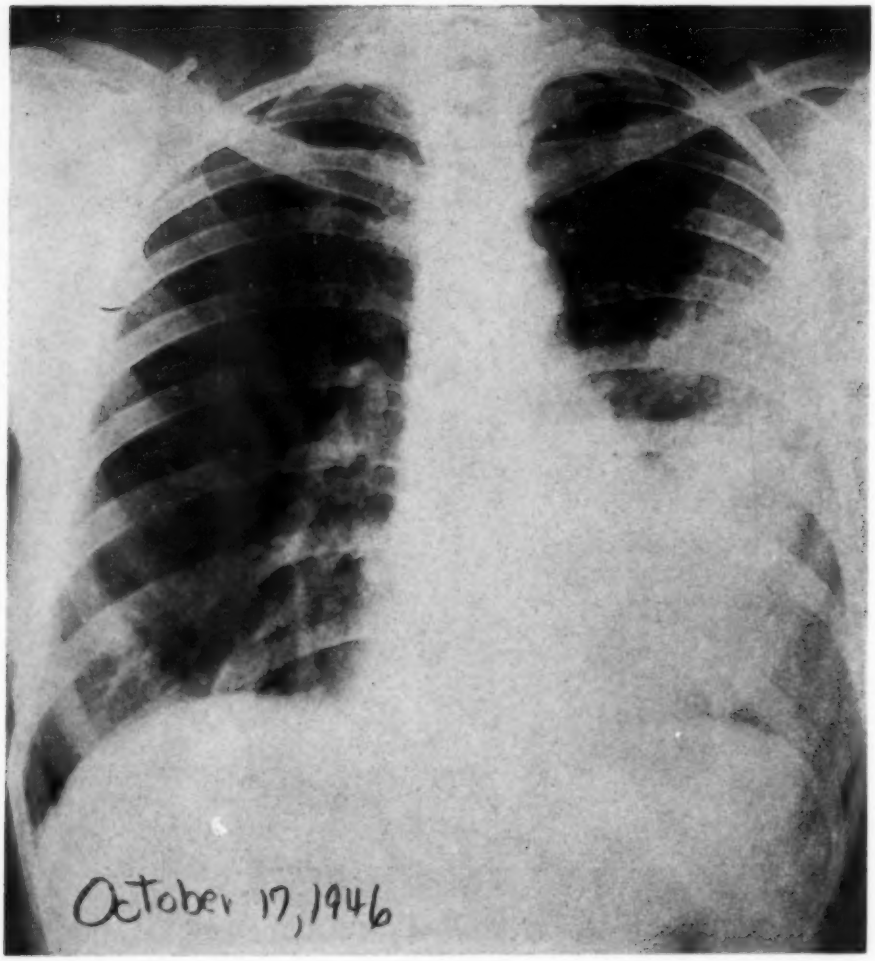


FIG. 2a. Patient P.Be. Forty-two year old white female. Confluent pneumonic infiltration, mostly in pectoral and lingular segments of left upper lobe. Prior roentgen-ray within three months had shown minimal infiltration; greatest part of pneumonic extension known to have occurred within one month. Note cavity at level of third anterior rib.

All such satisfactory immediate results in adults occurred in patients with patchy pneumonic or confluent pneumonic lesions (groups Ia and Ib, table 1),

* The term *cavity closure* is used to designate instances in which cavities, recognizable on at least two stero-roentgenographic examinations, were no longer seen in two or more subsequent examinations. The term *sputum conversion* is used to describe instances in which tubercle bacilli, previously demonstrable and usually abundant in the sputum, could no longer be detected on culture or direct examination of concentrated sputum or gastric washings on two or more successive observations.

examples of which are shown in figures 1 and 2. The result in the child with a progressive primary lesion was also satisfactory. No instances of such extensive roentgenologic clearing and cavity closure were observed in the patients with caseo-cavernous lesions (group Id, table 1). Two of the

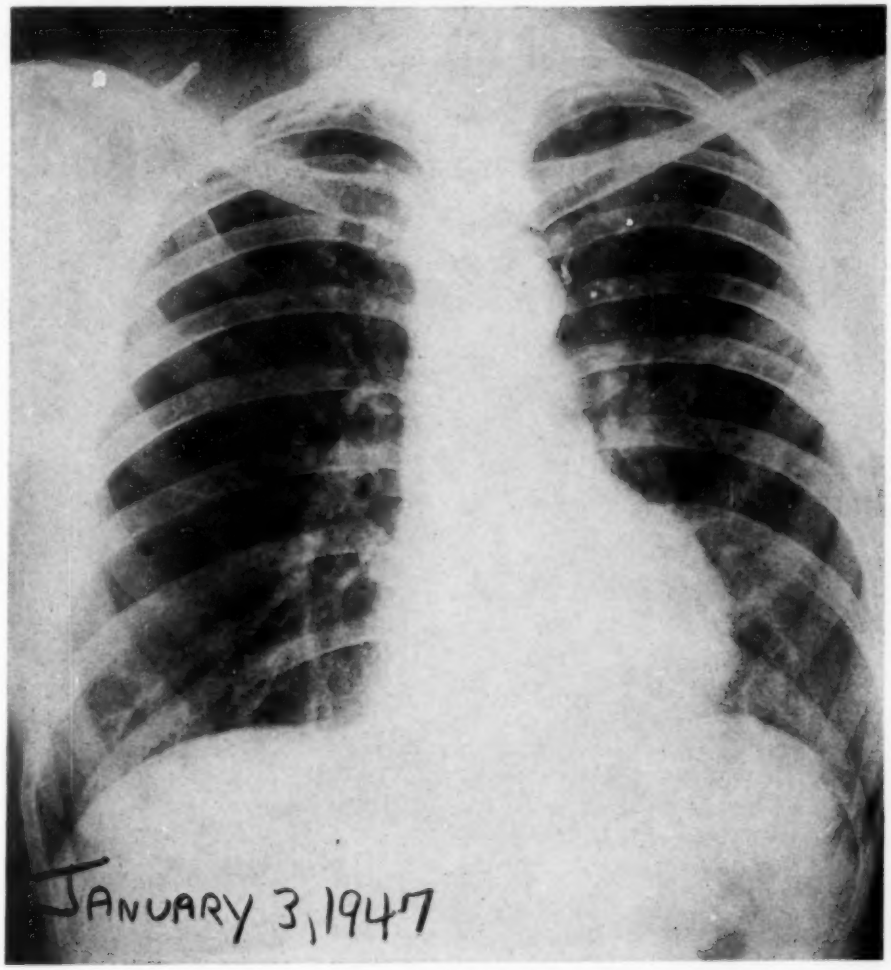


FIG. 2b. Patient P.Be., after streptomycin treatment which was discontinued on sixty-fourth day because of moderately severe skin reaction. Note cavity.

patients who attained satisfactory early remissions * received treatment for 120 days, two were treated for 63 to 120 days, and in the remaining five (including the one patient who received only 1 gram daily) the total period

* The term *early remission* is here used to designate the status of patients who were: asymptomatic, afebrile, discharged no tubercle bacilli, had stationary or regressive lesions by roentgenography, and cavity was not present; this condition having persisted for more than one but not necessarily as long as the three months required by official N. T. A. Diagnostic Standards for the designation of *apparently arrested.*

of streptomycin therapy was only 42 days. There was no evidence that either the confluent pneumonic lesions or the cavities in these cases were complicated by the presence of bronchial obstruction. Bronchoscopy was necessarily omitted in the most acute cases because of the danger of spreading the disease, but the physical signs excluded with reasonable certainty the

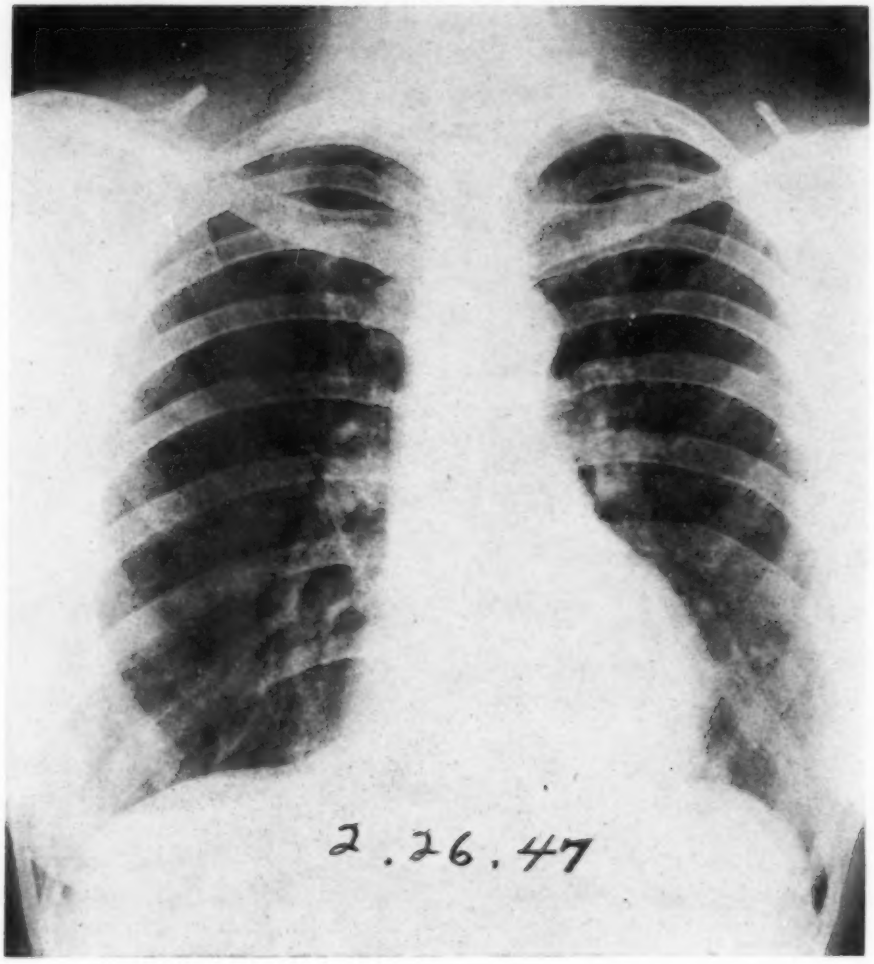


FIG. 2c. Patient P.Be., two months later. Note further improvement with disappearance of cavity although treatment was not resumed. Dose 3.0 gm. daily.

possibility that confluent shadows were caused by atelectasis or "drowned lung" secondary to bronchial obstruction. The halting of the onward progress of the lesion and the onset of roentgenologic clearing occurred uniformly within two to four weeks of the institution of the antimicrobial therapy. The speed with which extensive roentgenologic clearing and

cavity closure were completed in six of the patients equalled or exceeded the most rapid improvement hitherto observed by the present investigators on bed rest alone. In the others, although the onset of improvement appeared early, the greater part of the roentgenologic clearing did not occur until after the first six weeks of the antimicrobial therapy. It is of interest that the clearing which occurred in these latter patients in the second and third

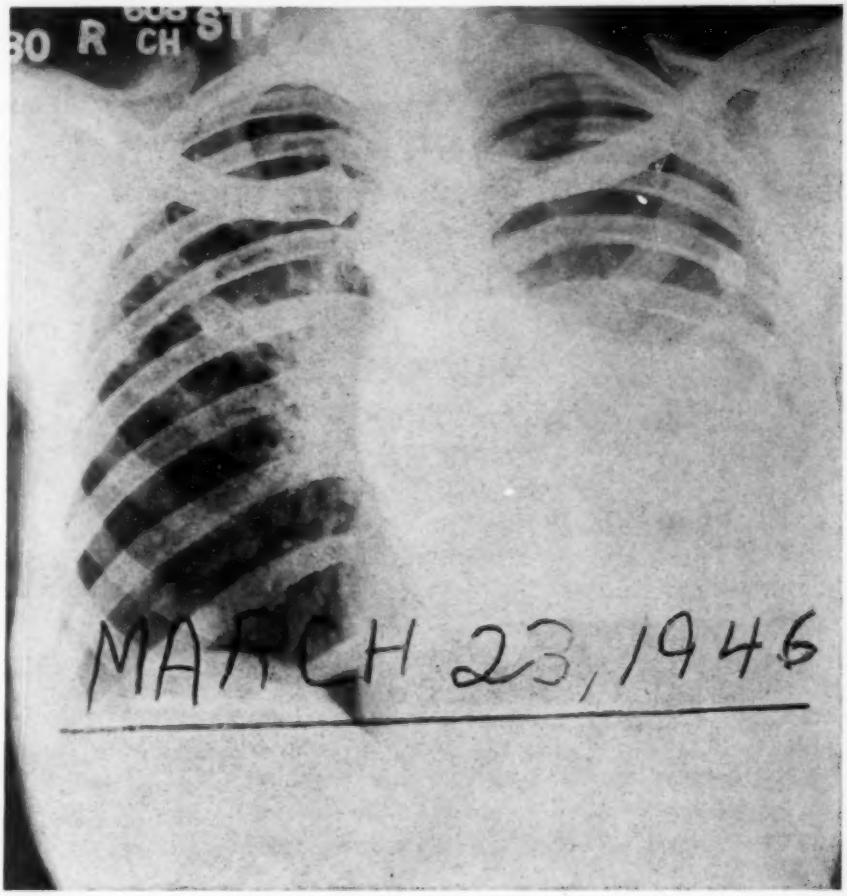


FIG. 3a. Patient B.Ir. Thirty-three year old colored woman. Before streptomycin treatment. Confluent tuberculous pneumonia of left lower lobe with patchy pneumonic infiltration in opposite lung.

months after the start of therapy was equally extensive whether the streptomycin therapy was continued for 120 or for only 42 days.

In general, the clearing of the presumed exudative lesions and the disappearance of the cavities proceeded simultaneously. In several instances, however, extensive resolution preceded cavity closure and the cavities became less prominent as a result of the disappearance of the surrounding zone of

inflammation. The period from the start of antimicrobial therapy to the closure of all cavities (in each individual patient) ranged from three to 12 weeks in these predominantly exudative infections.

The rate of disappearance of tubercle bacilli from the sputum and gastric contents varied according to the speed with which the lesions resolved and

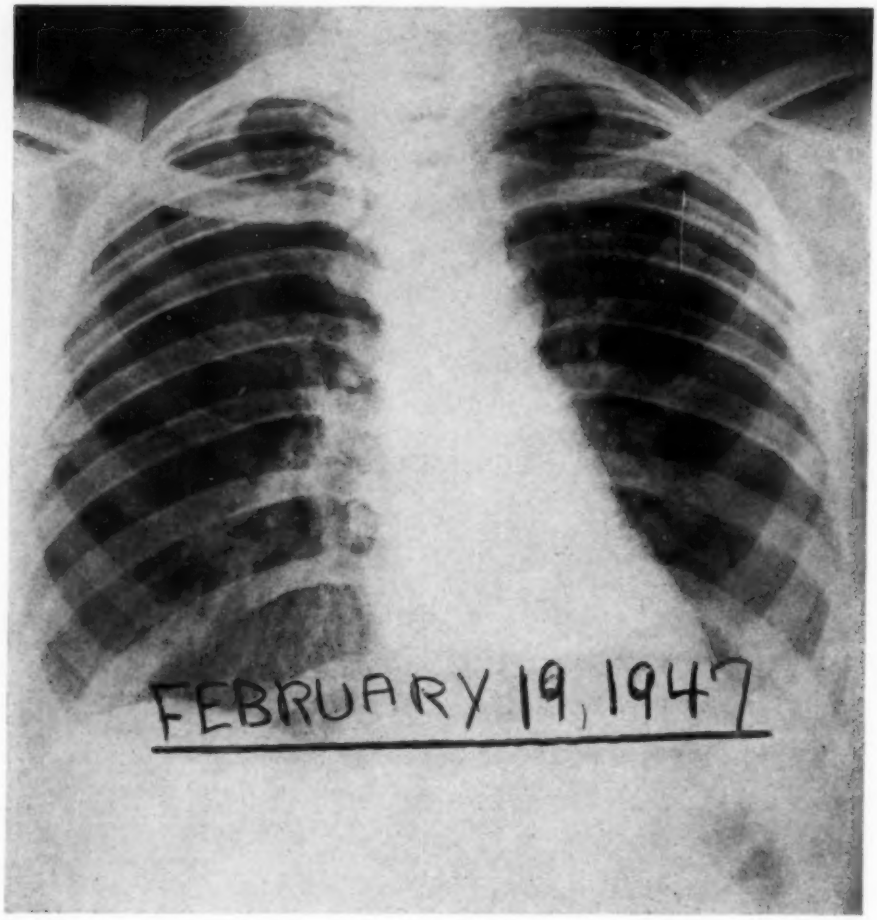


FIG. 3b. Patient B.Ir. 11 months later. Much of the clearing had taken place before end of 120 day course of streptomycin but improvement continued after end of therapy. This patient later relapsed.

cavity closure occurred. In some instances, the first few negative examinations were followed by one or more that were positive, which in turn were followed by several or more negative observations. Recurrence of occasionally positive sputum, with bacilli present in relatively small number, is not uncommon after initial conversion by any method of treatment, and does not in itself indicate eventual therapeutic failure. Using the arbitrarily

determined value of two successive negative smears or cultures, tubercle bacilli "disappeared" from the sputum and gastric washings of these nine patients between the second and the eighth week after the start of streptomycin therapy.

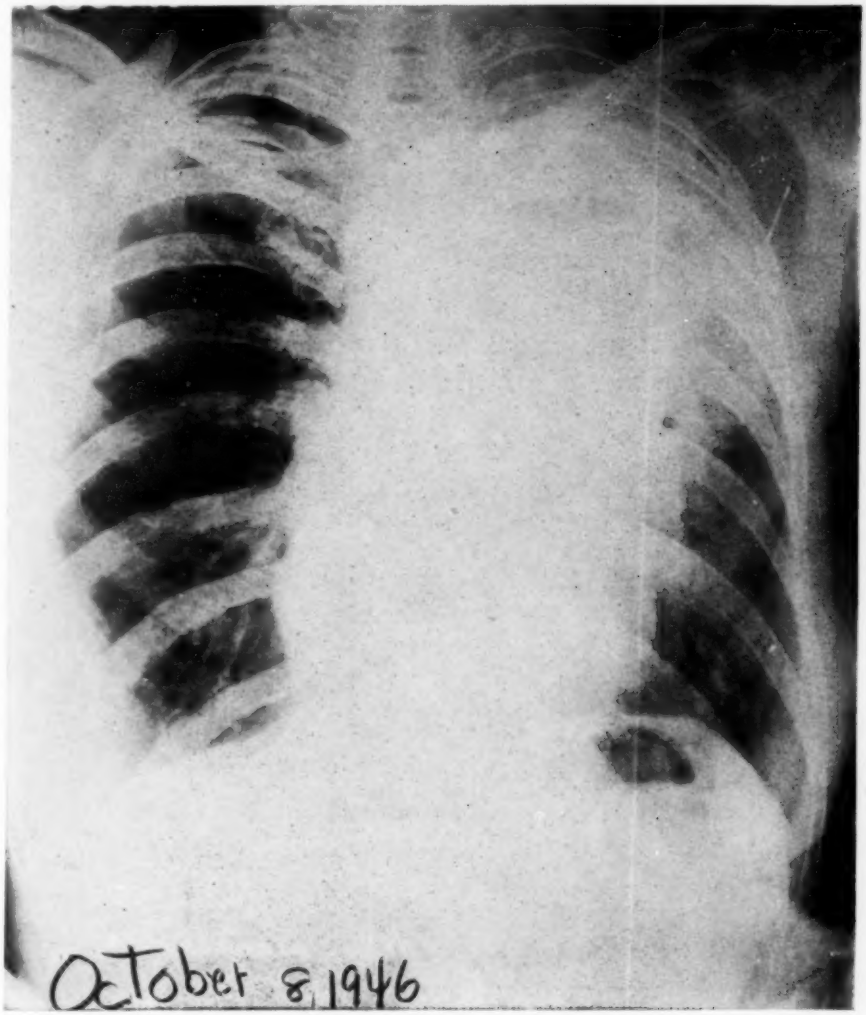


FIG. 4a. Patient G.Wi. Thirty-nine year old colored woman. Confluent pneumonic involvement of left upper lobe of approximately two months' duration. Bucky film of this date (not shown) revealed considerable excavation in infraclavicular region. Temperature ranging above 39° C.

All of the patients were confined to bed for approximately five months after cavity closure. This measure was adopted both because of the potential seriousness of the lesions before treatment and the lack of knowledge concerning the stability of drug-induced remissions. The remissions have been

maintained for more than six months in four patients who might therefore be classified as *arrested,* except that the criteria regarding physical exercise have not been fulfilled.

*Relapse:* Clinical, roentgenologic and bacteriologic evidence of relapse appeared within 10 months of the completion of therapy in three of the nine

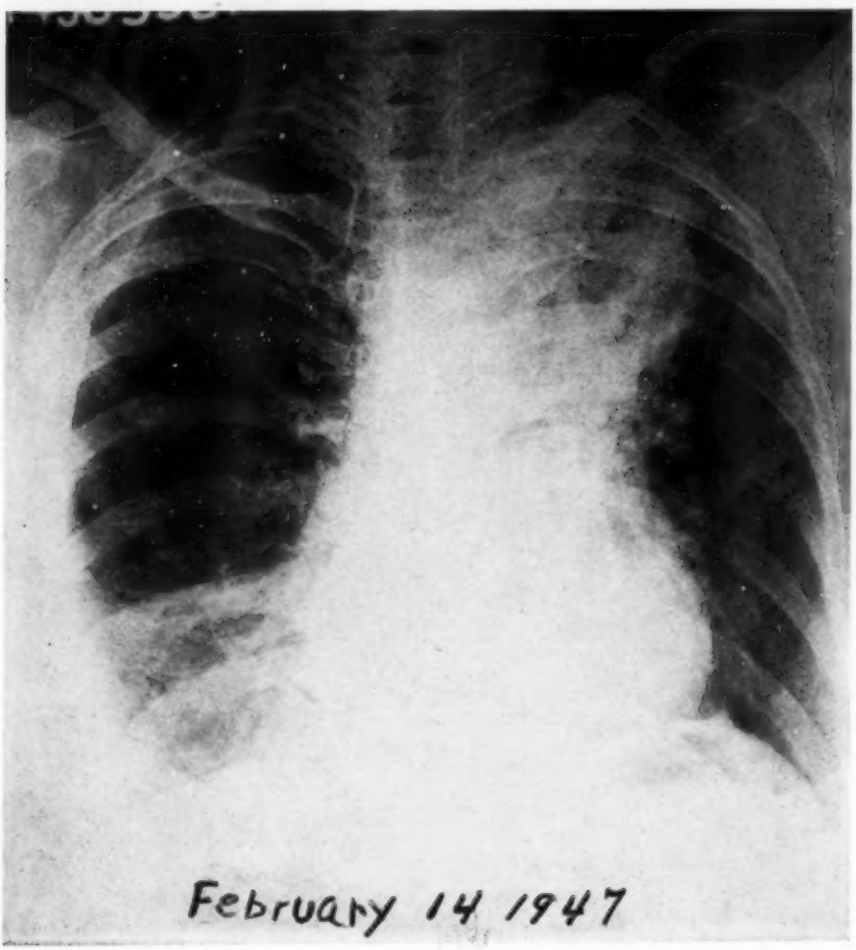


FIG. 4b. Patient G.Wi., after 120 day course of streptomycin. Note extensive regression but persistence of dense infiltration in apical region with irregular cavities.

patients who had attained early remissions. Two of the relapses appeared between the first and third months after streptomycin therapy had been discontinued. As both of these occurred despite the continuation of a regimen of bed rest, they must be considered as therapeutic failures. They have subsequently received collapse therapy. The third patient was a 33 year old colored woman (figure 3), in whom reactivation of the disease oc-

curred under circumstances of grossly inadequate rest and nutrition, 10 months after the cessation of streptomycin. Antimicrobial therapy was not reinstituted in any of these patients who relapsed after control of the infection had apparently been attained.

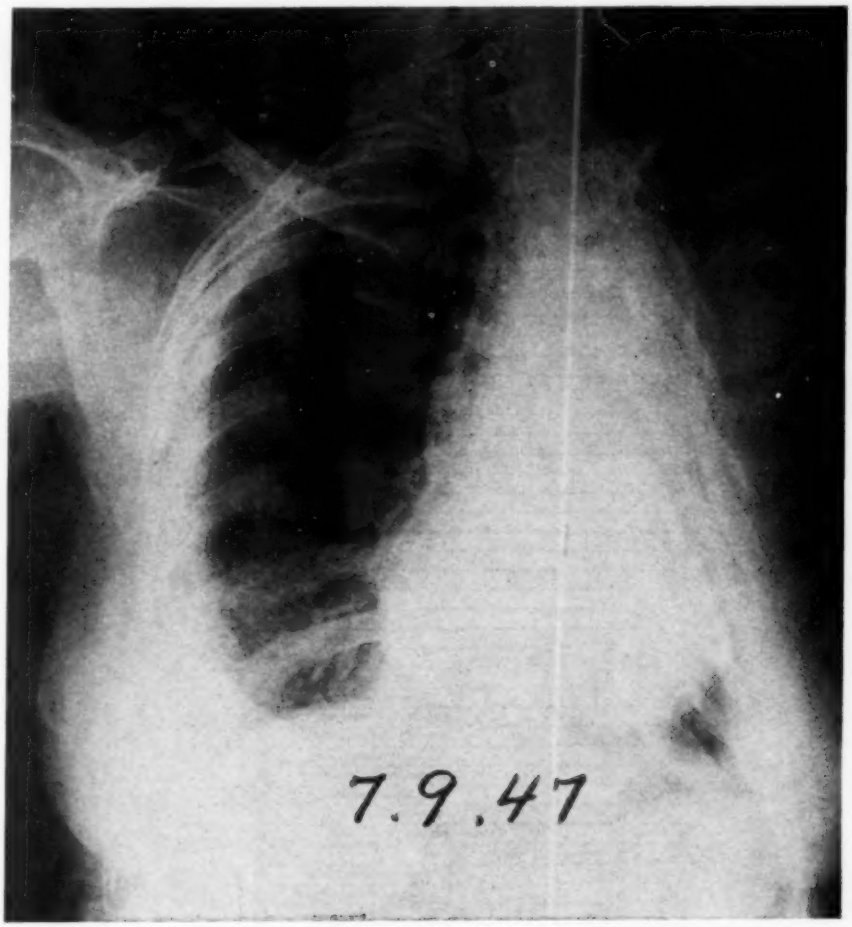


FIG. 4c. Patient G.Wi., after thoracoplasty operation. The pleural thickening on the right is result of pleurisy with effusion 3½ years earlier.

*Continued Quiescence without Cavity Closure.* In six of the 18 patients in the group with predominantly exudative lesions there was a variable degree of roentgenologic clearing and cavity shrinkage which did not continue to the point of complete closure. Although the change in the status of the disease when therapy was discontinued was not as favorable in these as in the patients who attained satisfactory early remissions, the total improvement was usually impressive. In all instances, the disease had been

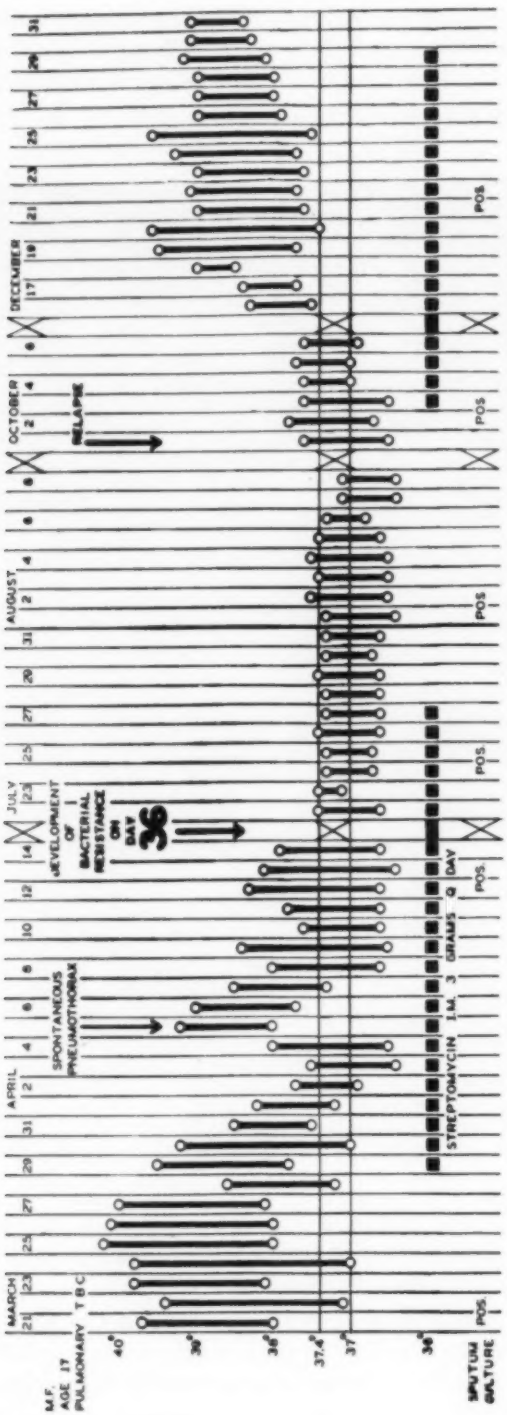


FIG. 5a. Patient M.Fl. Seventeen year old colored boy with caseo-cavernous disease of at least 10 weeks' duration. Temperature chart.

actively progressing before the streptomycin treatment and for various reasons collapse therapy had been considered inadvisable. Three received collapse therapy subsequent to the streptomycin. In all three the collapse therapy (pneumothorax 1, thoracoplasty 2) has been initially successful

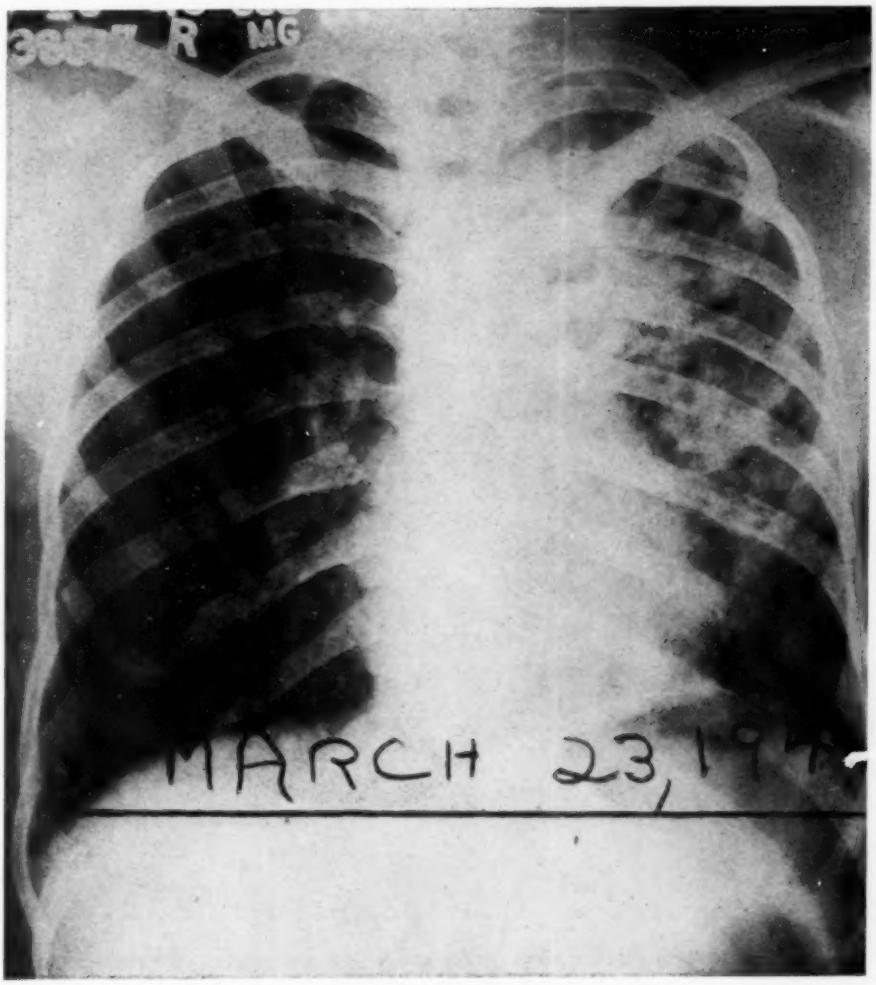


FIG. 5b. Patient M.Fl., roentgen-ray before treatment. Note multilocular cavities occupying almost entire apical region and punched out smaller cavities below.

with prompt cavity closure and sputum conversion. This is of particular interest because the disease prior to streptomycin had in each instance been considered too acute to justify the use of such procedures. A representative example is illustrated in figure 4.

*Improvement, Chiefly Symptomatic, Followed by Further Excavation and Resumption of Progressive Course.* In three of the total group of 18

patients with predominantly exudative lesions, the course under streptomycin therapy consisted of an initial period of clinical improvement, followed by further excavation of the diseased area of variable extent, and eventual resumption of steadily progressive tuberculosis. All of the three patients had large or multilocular cavities within confluent pneumonic segments

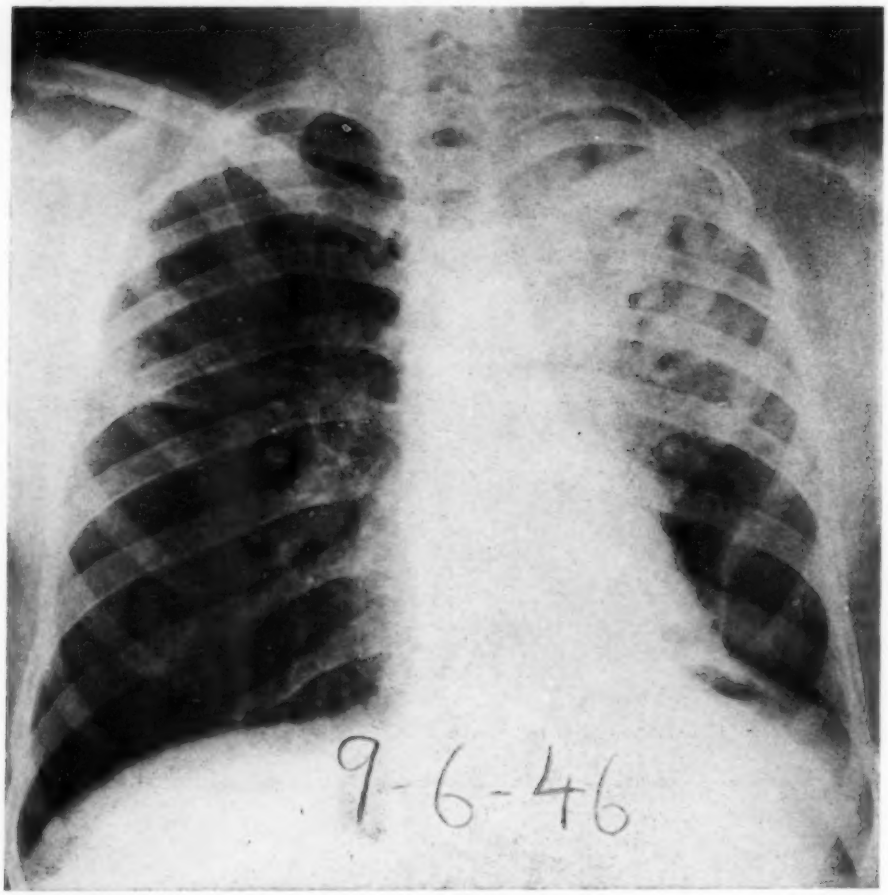


FIG. 5c. Patient M.Fl., five weeks after end of 120 day course of streptomycin. The apparent contraction of the extensively involved left lung may be due in part to the therapy but can also be attributed to an intercurrent spontaneous pneumothorax. Spread of an originally small focus in the opposite lung is now apparent.

which had apparently progressed to the stage of massive caseation (group Id, table 1).

A representative example of this type of case may be seen in figure 5. The patient was a 17 year old colored boy who had been acutely ill with a confluent tuberculous pneumonia for 10 weeks before streptomycin therapy was started. An abrupt defervescence occurred within 72 hours of the

institution of antimicrobial therapy. Several days later, however, the temperature again rose in association with a spontaneous pneumothorax. Despite the acute nature of the underlying process, only a small sterile pleural effusion accumulated. The temperature promptly fell to normal as the air and fluid resorbed and the hydropneumothorax space became obliterated.

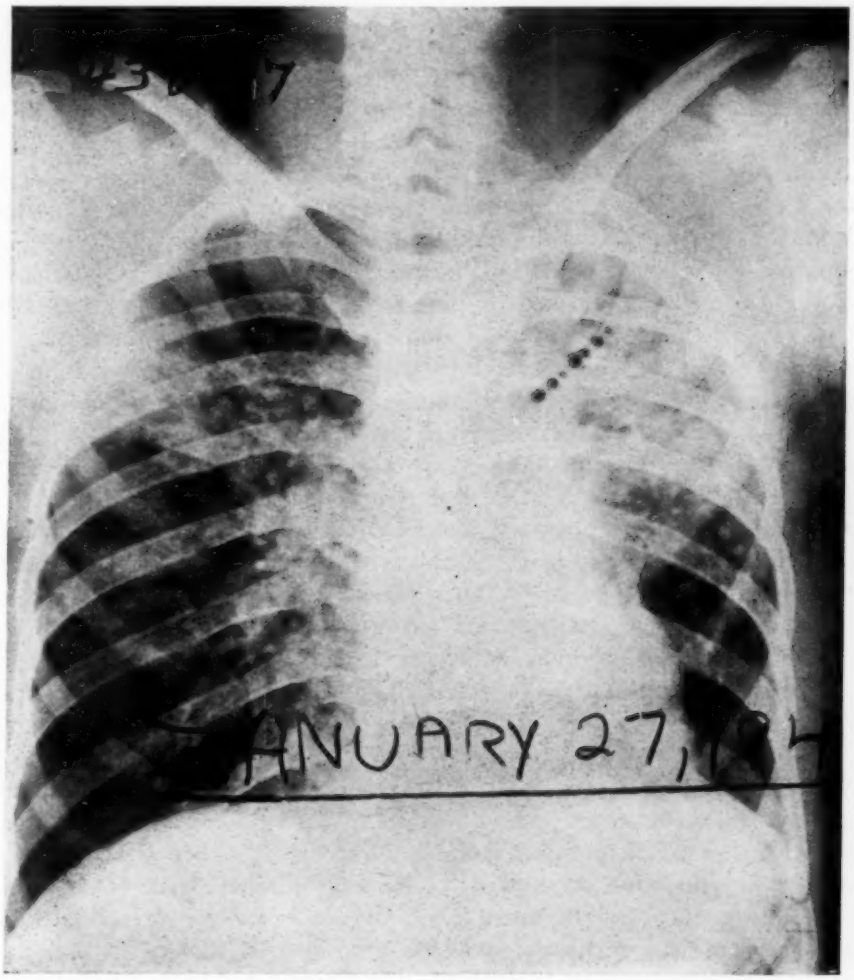


FIG. 5d. Patient M.Fl., further progression despite resumption of streptomycin after bacterial resistance had been observed in vitro.

Throughout the ensuing three months of streptomycin therapy, the initial symptomatic improvement was maintained. There was no roentgenologic evidence that new areas of lung were becoming involved, but no significant objective improvement was evident. All cultures of tubercle bacilli isolated subsequent to the thirty-fifth day of therapy were highly resistant to

the action of streptomycin in vitro. Five weeks after the completion of the first course of drug therapy, reactivation of a tiny area of disease in the contralateral lung was evident by roentgenography. Although streptomycin therapy was promptly re-instituted, the infection assumed a rapidly progressive course which terminated fatally five months after the first appearance of relapse.

A similar course was observed in the second patient in this group who also has died. The third patient, though still living at the present writing, is given a hopeless prognosis and is virtually moribund. In all three, strains of tubercle bacilli highly resistant to streptomycin in vitro appeared during therapy.

*Summary of the Results in the Group with Recent Predominantly Exudative Pulmonary Tuberculosis with Early Cavitation.* Eighteen patients with various forms of early predominantly exudative tuberculosis received streptomycin for periods ranging between 42 and 120 days. Satisfactory early remissions were attained by nine of the group. All of the nine had patchy or confluent pneumonic lesions which, although extensive, had apparently not caseated massively or excavated large segments of lung substance. In two instances, the early remission was followed by relapse within two months of the completion of streptomycin therapy. In six patients, the institution of streptomycin therapy was followed by an impressive degree of improvement which fell short of full remission. In three patients whose disease had presumably progressed to extensive caseation, a short period of improvement was followed by the resumption of a rapidly progressive course.

In the total of 18, there are seven whose disease was apparently controlled for six months or longer without the aid of collapse therapy. An additional five have had collapse therapy which in every instance has been apparently successful, although the patients would all have been regarded as unfavorable risks prior to the improvement under streptomycin.

*Group II. Chronic Pulmonary Tuberculosis with Fibro-Cavernous Secondary Changes.* In contrast to the response of the early predominantly exudative cases, the improvement was relatively small in the group of patients with disease of more chronic type which was either known to be of relatively long duration or showed roentgenographic evidence of established and extensive fibrosis. In most, exudative lesions were present also but this component was relatively small or associated with extensive involvement of chronic character. The results are shown in table 1, group II.

Of the 18 patients in this group, 16 received the 3.0 gram daily dose and two received the 1.0 gram dose. The symptomatic response, as might be expected, was seldom impressive and never dramatic. Likewise, the character of the signs elicited on examination of the lungs was not so strikingly altered, although the number of râles usually diminished appreciably during the streptomycin treatment. In all but one of the 18 patients, however, the introduction of streptomycin therapy was followed by roentgenologically demonstrable regression of some of the infiltrative process. There was

usually also a definite reduction in cavity size. In several instances in which persistence of cavitation was associated with endobronchial disease, a rapid

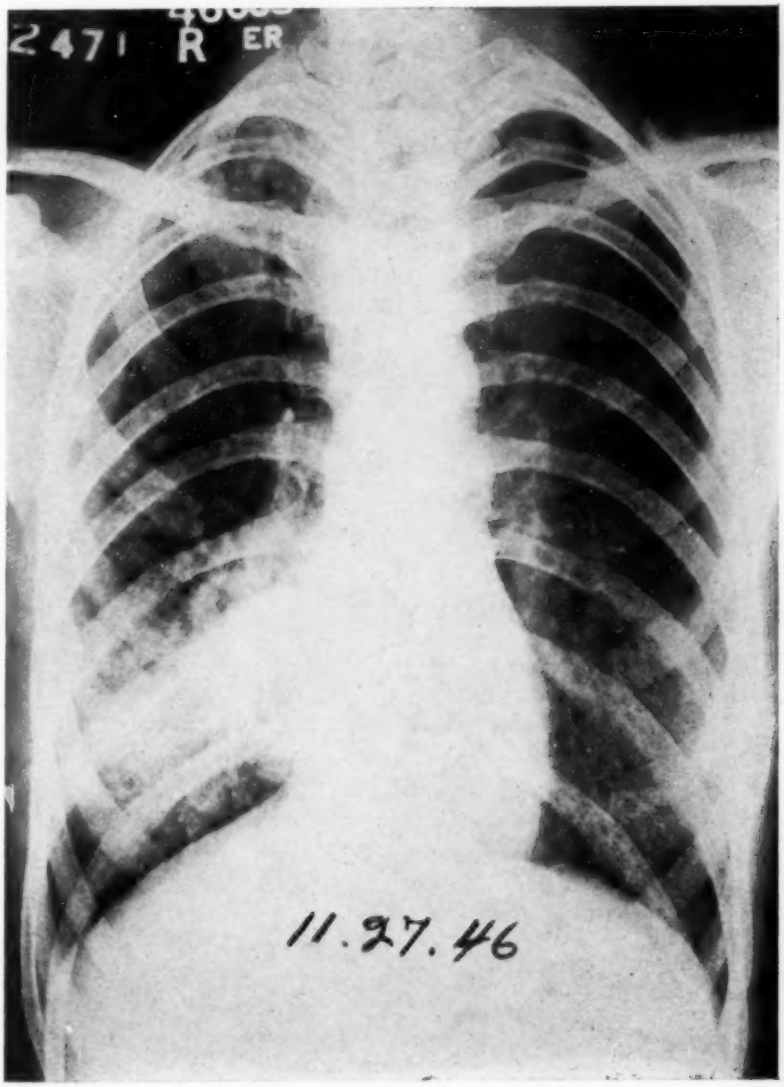


FIG. 6a. Patient C.McC. Before streptomycin treatment. A 19-year old white woman with extensive involvement of right lung of unknown duration. A febrile episode two months before was possibly related to spread of the disease. At start of therapy had been afebrile for seven weeks. No clearly defined cavitation.

shrinkage of the cavity occurred, presumably as a consequence of regression of the bronchial lesion.

Satisfactory early remissions were observed in only four patients, of whom three attained both cavity closure and sputum conversion. The

fourth had no cavity clearly discernible to begin with. This patient is of particular interest because the clearing, which was ultimately very satisfactory, did not begin to take place appreciably until after treatment had been

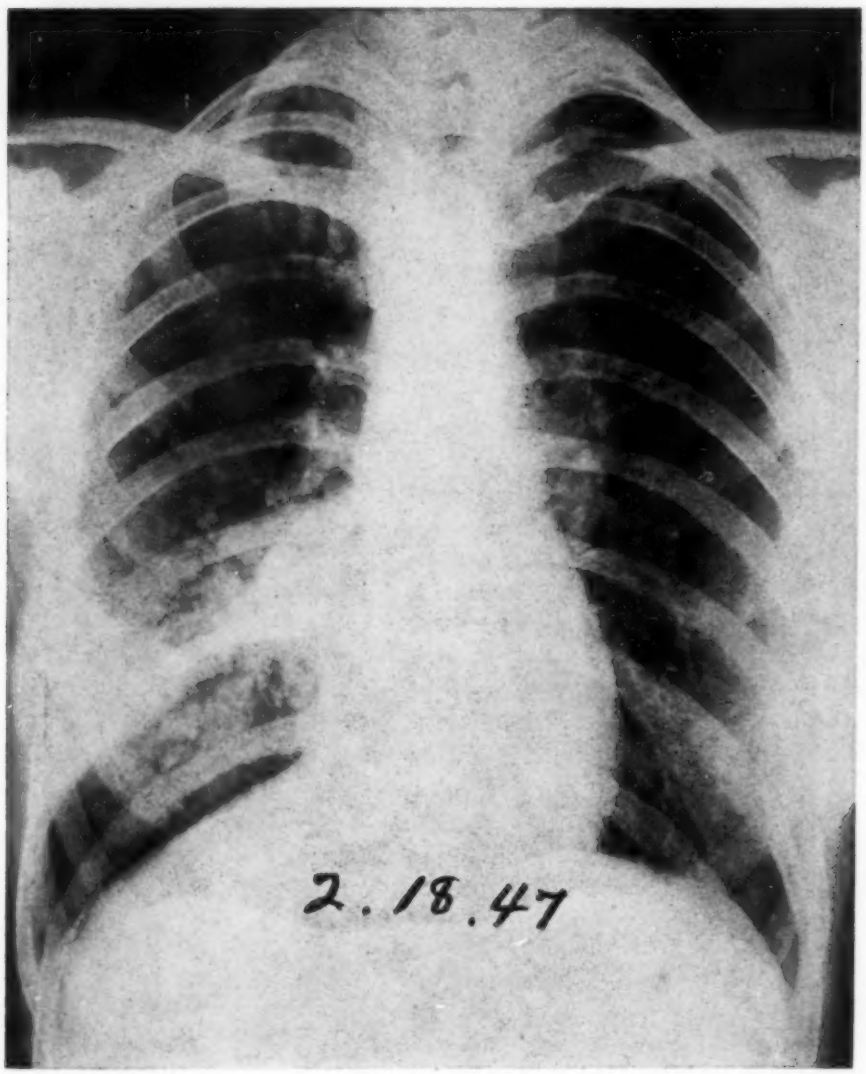


FIG. 6b. Patient C.McC., on seventy-fourth day of 90 day course of treatment. Note lack of any appreciable change at this time.

concluded, yet after regression had started it proceeded with considerable rapidity (figure 6). A fifth patient (table 1, group II) became sputum negative but there was persistence of an obvious cavity. This patient was one among four who were subjected to thoracoplasty. Apparent cavity

closure was accomplished in each, but sputum conversion followed in only two of the four. It is noteworthy that in these, as in the patients in the more acute group previously described, thoracoplasty had been considered

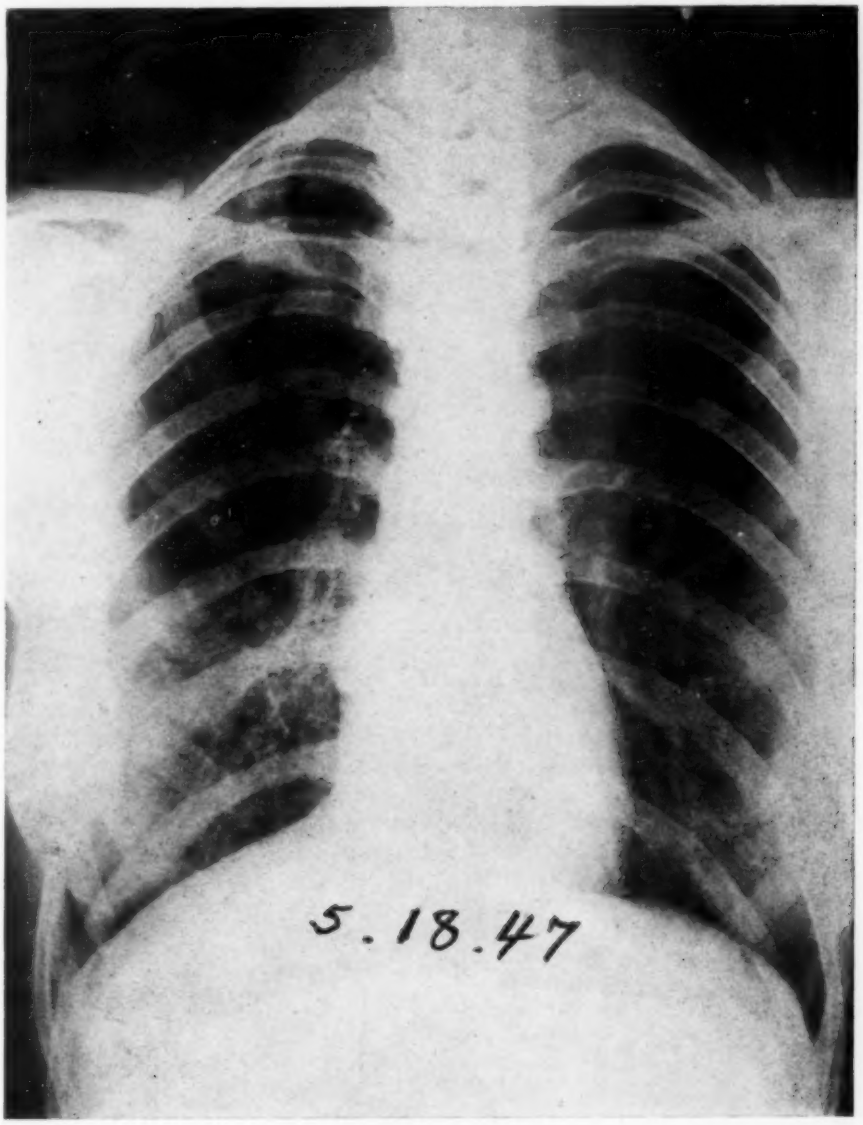


FIG. 6c. Patient C.McC., two and one-half months after end of streptomycin therapy, showing considerable "delayed resolution."

inadvisable prior to streptomycin because of actively advancing lesions in one or both lungs. Two did not appear as if they would ever be suitable candidates for the operation and in the other two the operation could

scarcely have been considered feasible within six months with the best fortune under standard treatment. The improvement during streptomycin treatment was sufficient to make operation appear feasible within eight to 12 weeks and it was accomplished in all without untoward developments, such as post-operative spread. The first stage operation was not performed in

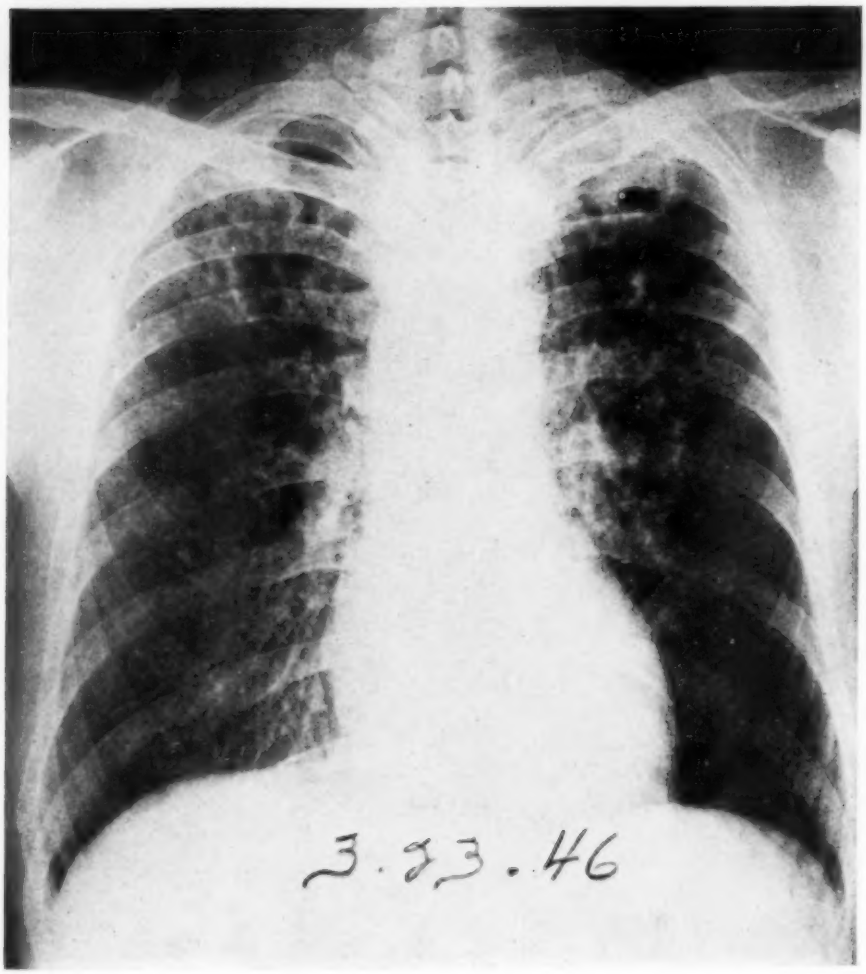


FIG. 7a. Patient J.Sa. A 53 year old white man with chronic fibro-cavernous involvement of both lungs. Before streptomycin treatment.

any instance until it appeared that the maximum regression and cavity shrinkage which was to be anticipated had occurred.

In the remaining 10 of the 18 patients with chronic fibro-cavernous lesions, a period of symptomatic and minor roentgenologic improvement observed during the early weeks of streptomycin therapy was followed by a

return to the pre-treatment state or an actual extension of the process. The loss of the apparent gain under antimicrobial therapy was preceded, in every instance, by the appearance of strains of tubercle bacilli which were highly resistant to streptomycin in vitro. In addition, and presumably unrelated to the drug-resistance, certain of these cases became complicated by such incidents as profuse hemorrhage or spontaneous rupture of the lung.

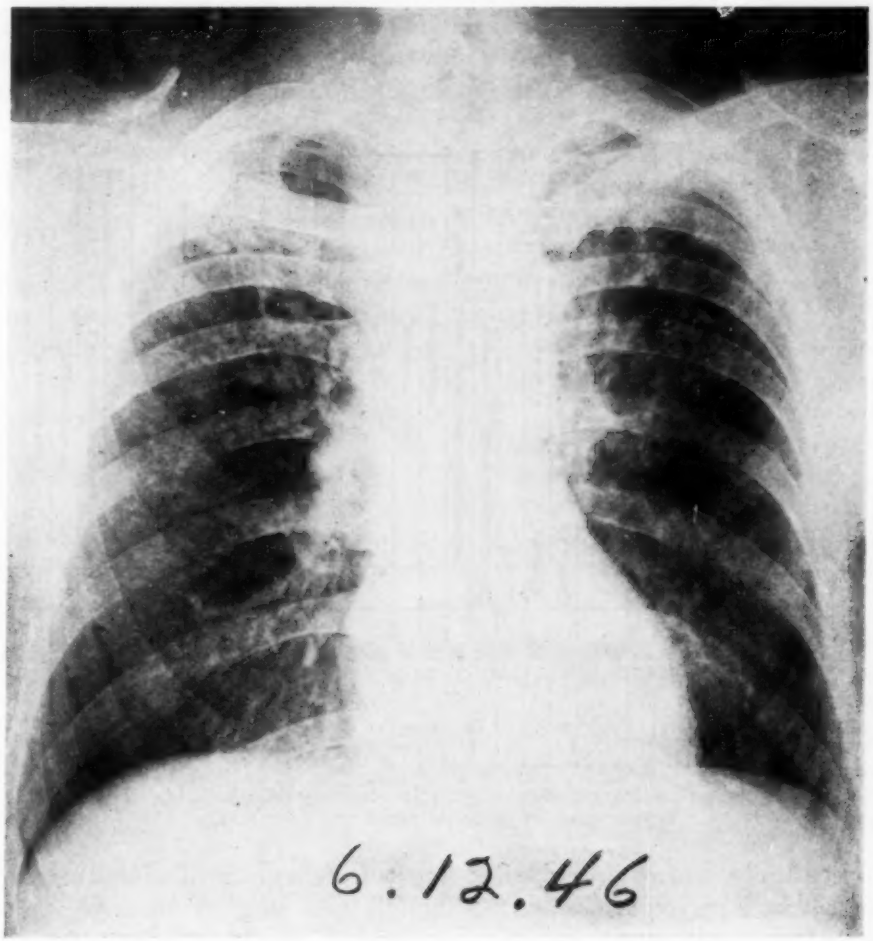


FIG. 7b. Patient J.Sa., early in third month of treatment. Note contraction of cavities.

A representative example of the type of therapeutic failure observed in chronic fibro-cavernous tuberculosis may be seen in figure 7.

The patient was a 52 year old man with bilateral chronic predominantly proliferative tuberculosis with three cavities, ranging from 2 to 4 cm. in diameter. During a four month period of observation on bed rest before streptomycin therapy, there had been essentially no change in the extent

of involvement or the size of the cavities. The patient had only mild toxemic symptoms with low grade fever. In the first 30 days of antimicrobial therapy, the fever disappeared and there was roentgenologic evidence of slight regression of the bilateral infiltrations with a definite reduction in the size of all three cavities. On the sixty-eighth day of streptomycin therapy, tubercle bacilli isolated from the sputum were highly resistant to streptomycin in vitro as were all cultures obtained subsequently. Although this development was not immediately followed by any change in the condition of the patient, on the seventy-third day of drug therapy the left lung spontaneously ruptured. A tuberculous empyema developed which was

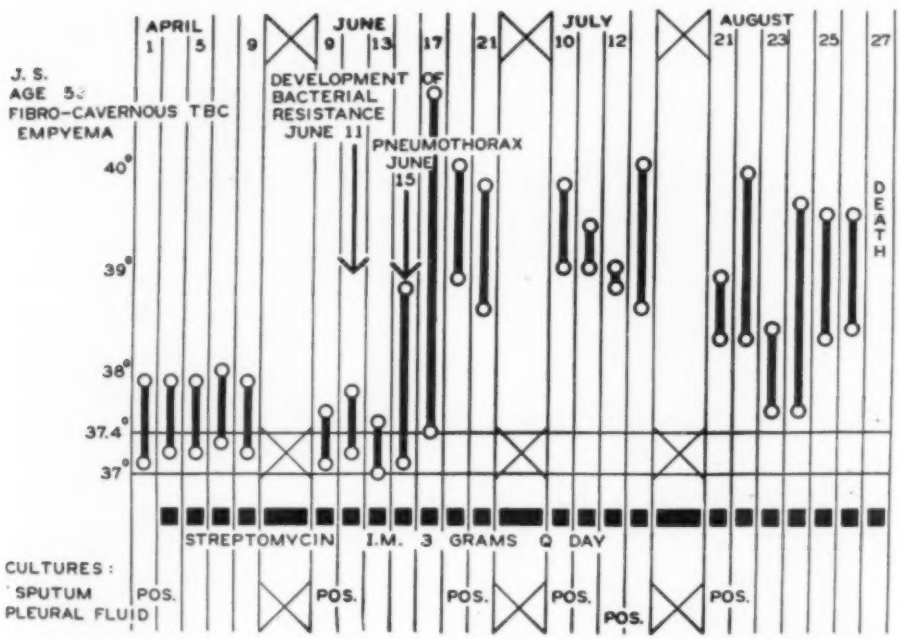


FIG. 7c. Patient J.Sa., temperature chart. Spontaneous pneumothorax occurred after development of bacterial resistance (see text).

unsuccessfully treated by repeated aspirations and instillations of streptomycin in 1 per cent solution. Although open surgical drainage was instituted and maintained and the antimicrobial therapy continued, the infection (with drug-resistant tubercle bacilli) assumed an acute febrile course which terminated fatally on the one hundred thirty-sixth day of streptomycin therapy.

In summary, of 18 patients with predominantly fibro-cavernous pulmonary tuberculosis, three attained cavity closure and sputum conversion during streptomycin therapy. A satisfactory result was observed in a fourth patient who had no definite cavitation to begin with and who attained sputum conversion with extensive regression of infiltration. Four patients, who

had previously been considered poor risks for thoracoplasty were sufficiently improved so that operation was performed without untoward complications. In the remaining 10 patients there was a variable degree of temporary improvement followed by resumption of progressive tendencies. None of these were suitable cases for collapse therapy after the failure of streptomycin to promote satisfactory remission had become apparent. In several instances collapse therapy might have been feasible had it been undertaken at the time of maximal improvement, before the disease reëntered an advancing phase.

*Laryngeal and Tracheobronchial Lesions.* Ulcerative lesions of the larynx or bronchi were present before streptomycin therapy in eight of the total group of 43 patients with pulmonary tuberculosis. Evidence of healing appeared in all of these lesions within one week of the start of therapy and the process was usually completed by the end of the second month. In one patient, a bronchial lesion subsequently recurred under streptomycin therapy at a time when the bacilli obtained from the sputum were streptomycin resistant in vitro. Lesions remained healed despite the development of drug-resistant bacilli, however, in two patients.

*In Vitro Streptomycin Resistance of Organisms Isolated from Patients with Pulmonary Tuberculosis.* The results of the in vitro determinations of streptomycin sensitivity of the organisms isolated from the patients with pulmonary tuberculosis were similar to the results previously reported for the group with generalized hematogenous infections.[1] Tubercle bacilli could be cultured regularly from 23 of 39 patients during and subsequent to streptomycin therapy. Most of the 16 patients from whom organisms were not obtainable during therapy represented instances in which cavity closure had also taken place.

There was a striking correlation between the appearance of in vitro streptomycin resistance and the duration of therapy. In 11 of the 23 patients who discharged bacilli regularly throughout therapy, the streptomycin was administered continuously for total periods of 75 to 120 days. In all but one of these infections, streptomycin-resistant * strains of tubercle bacilli appeared during the period of therapy and were isolated regularly thereafter. The exception was a patient from whom drug-resistant bacilli were not obtained until 51 days after the start of a second course of therapy or 244 days after the original institution of streptomycin. When these data are combined with the previously reported determinations on bacilli from the pulmonary lesions of miliary infections,[1] it may be seen that drug-resistant organisms were obtained from all but one of the 17 patients who continued to discharge bacilli throughout a period of therapy of 75 to 120 days.

In contrast to these findings, the appearance of drug-resistant strains of bacilli was observed in only one of the 11 patients who received only 42 days of therapy and who continued to discharge organisms throughout treat-

* To simplify the discussion the term "streptomycin-resistant" is used to designate strains of tubercle bacilli which are not inhibited by streptomycin concentrations of 500 micrograms per c.c.

ment. In seven of this group the organisms were tested at approximately 100 days after the start of treatment. Organisms from the remaining four infections were drug-sensitive at the completion of therapy but have not been tested thereafter. Seven of the 42 day cases received 3.0 grams of streptomycin daily and in the other four patients the total daily dose was only one gram. The one patient from whom drug-resistant organisms were obtained was on the 3.0 gram regimen.

Streptomycin-resistant strains of tubercle bacilli were observed as early as the second month of therapy in two of the pulmonary infections. In

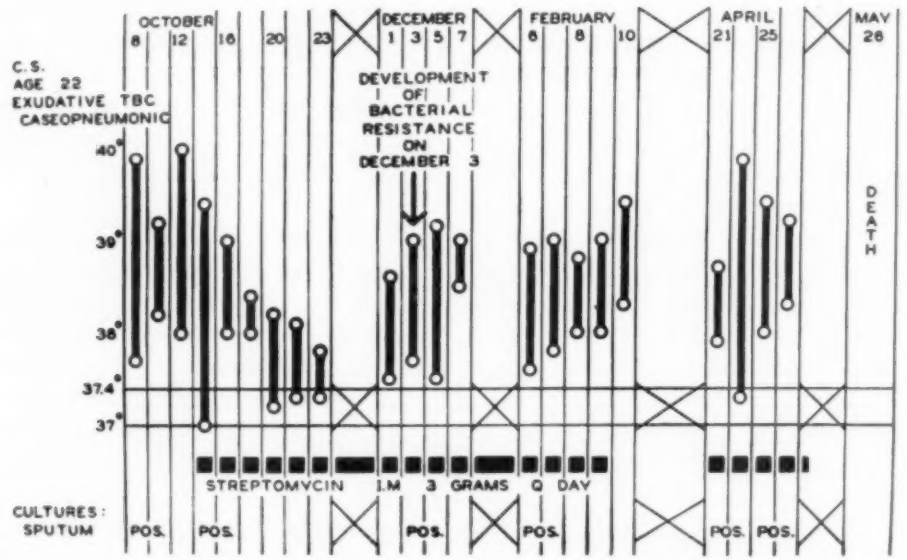


FIG. 8a. Patient C.St. Twenty-two year old colored woman. Temperature course showing early return of fever after initial response to streptomycin.

general, however, in the pulmonary infections as in the generalized hematogenous infections, the majority of the drug-resistant strains appeared in the third month of the streptomycin treatment. The disappearance of the phenomenon of in vitro drug-resistance was not observed. In one patient organisms which were resistant to streptomycin concentrations of 10 micrograms per c.c. but were sensitive to 15 micrograms per c.c. were isolated eight months after completion of the 120 day regimen. This patient had attained cavity closure during therapy so that no organisms had been obtained by culture after the first 31 days of treatment. In all four individuals from whom bacilli could be obtained regularly during the year after the start of drug therapy, the organisms were not inhibited by streptomycin concentrations of 500 micrograms per c.c.

*Correlation between in Vitro and in Vivo Streptomycin Sensitivity.* An apparent correlation existed between the course of a pulmonary infection during chemotherapy and the sensitivity of the bacilli to streptomycin in

vitro. In four of the 11 pulmonary infections from which drug-resistant bacilli were obtained, the discharge of organisms ceased soon after the first demonstration of the phenomenon. These were all instances in which the finding of resistant bacilli represented the last positive culture obtainable

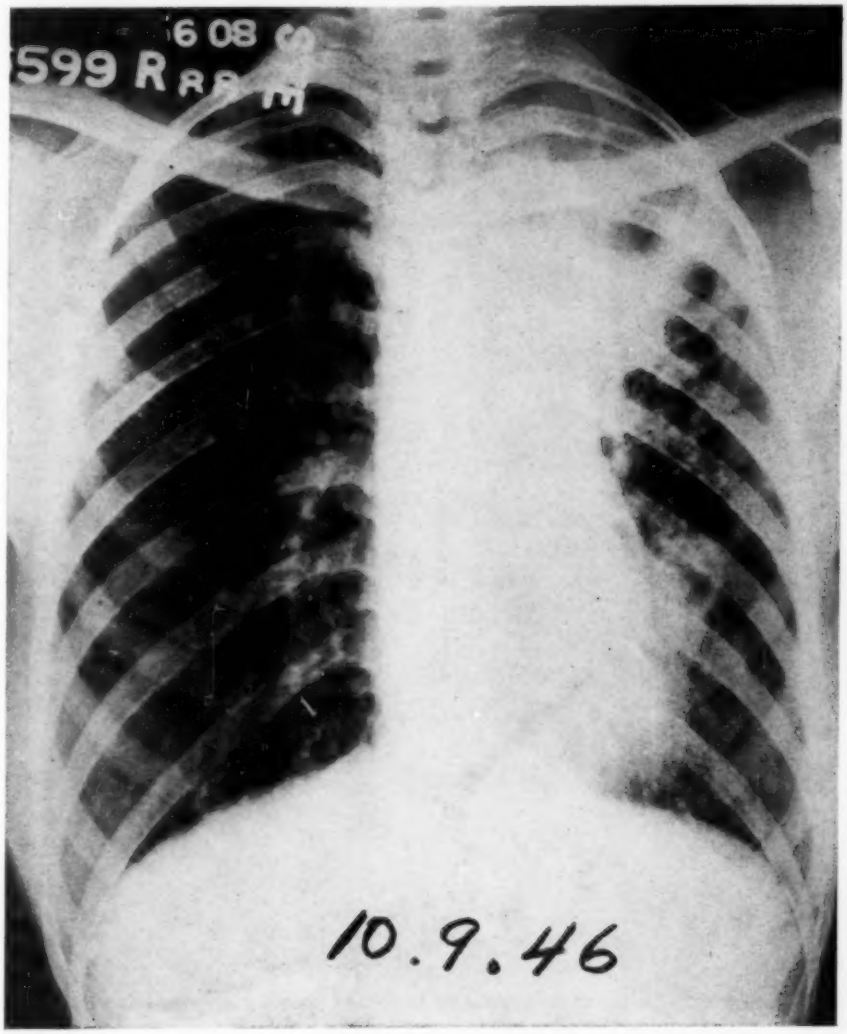


FIG. 8b. Patient C.St., chest roentgen-ray before treatment.

from a patient whose disease had regressed, or been converted by surgical collapse, to a state of non-infectiousness. In the remaining seven cases, however, the discharge of drug-resistant bacilli persisted throughout therapy and the post-treatment period of observation. During the first month of streptomycin therapy all of these seven patients had shown evidence of im-

provement although the change noted in one individual was not marked (figure 8). At a variable interval after the first appearance of drug-resistant bacilli, all seven cases resumed a progressive course. In four, the resumption of progression occurred during antimicrobial therapy and in the other three

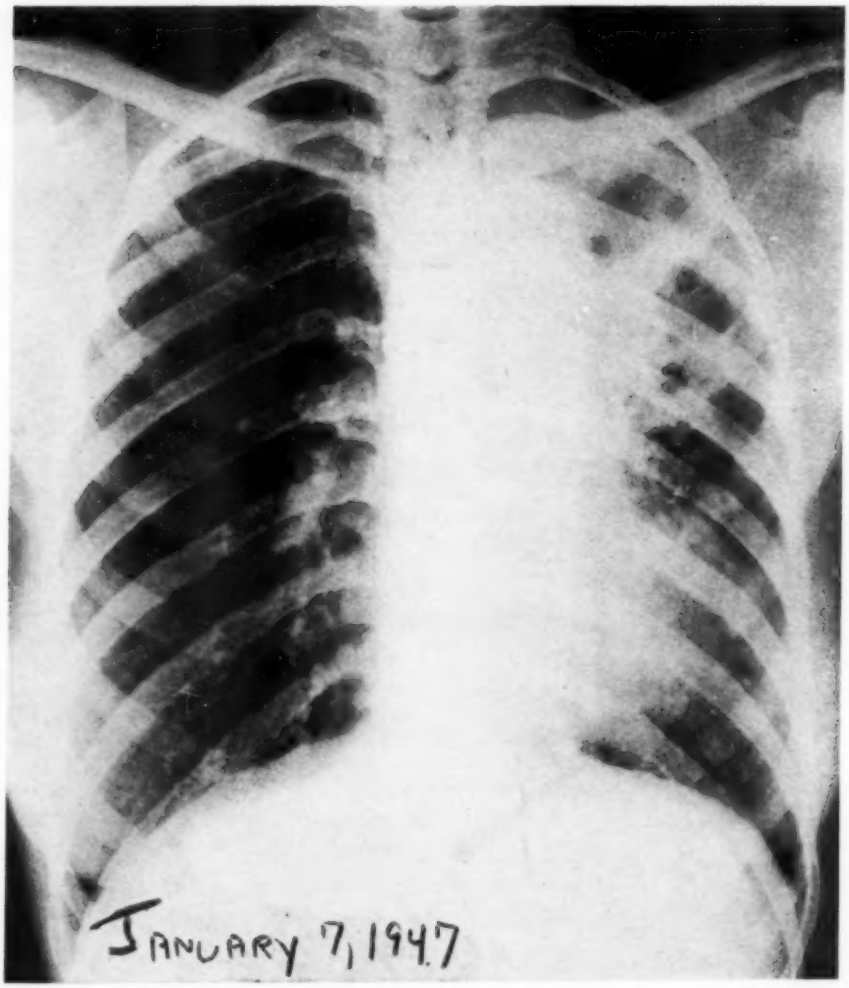


FIG. 8c. Patient C.St., after three months of treatment showing progression which occurred after development of bacterial resistance.

shortly after the cessation of therapy. In all seven the re-institution or continuation of streptomycin (3.0 grams daily) had no discernible effect upon the course. The tuberculosis continued to progress and in four instances the disease terminated fatally.

*Histopathologic Observations.* Postmortem examinations were performed on only two patients, both of whom had been discharging strepto-

mycin-resistant tubercle bacilli for several months before death. Study of the tissues revealed the characteristic changes of pulmonary tuberculosis without any unusual features which could be attributed to the streptomycin therapy.

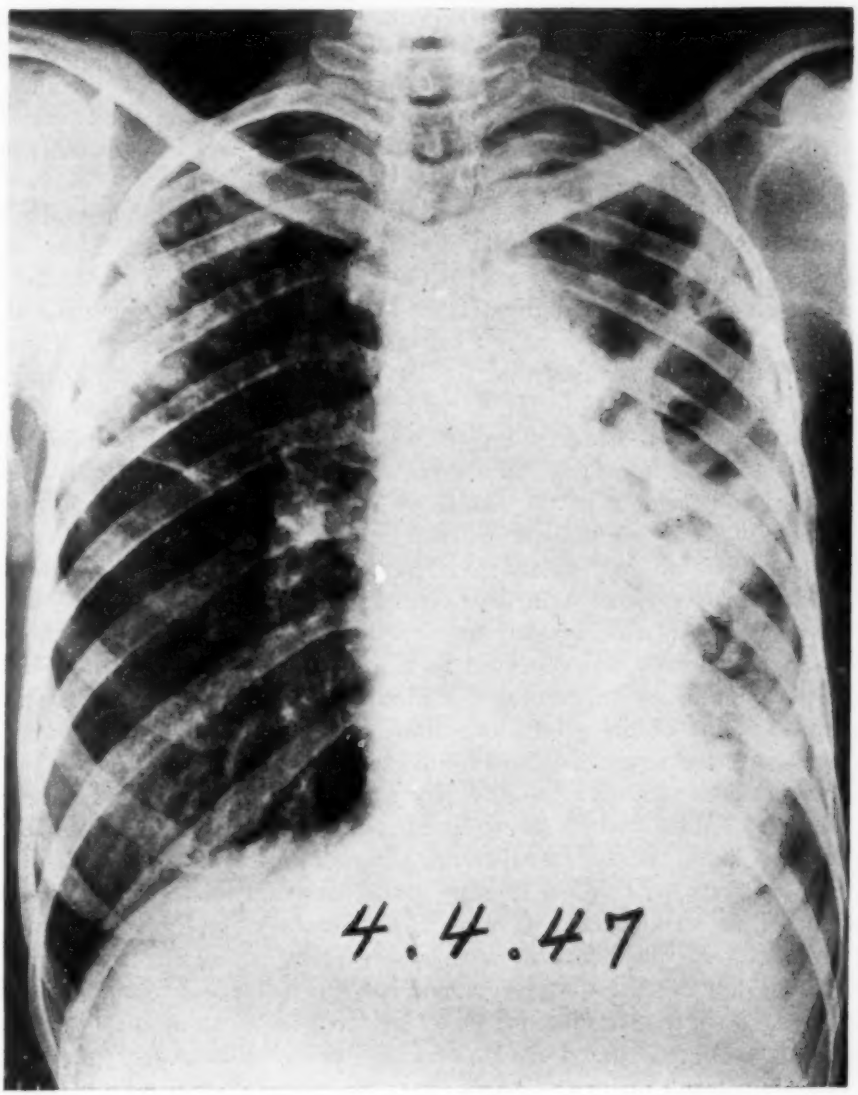


FIG. 8d. Patient C.St., further progression, uninfluenced by re-treating with streptomycin.

## DISCUSSION

It has been established both in experimentally infected animals [6] and in patients with the generalized hematogenous or the meningeal forms of the

disease [1, 3] that streptomycin can exert an effect upon tuberculous infections in vivo. Moreover, in these investigations a definite effect upon disseminated tubercles in the lung was noted. Thus it can also be considered to be established that streptomycin is capable of exerting its antimicrobial action on at least one type of tuberculous lesion in the lung.

In contrast to the conditions which obtain for miliary tuberculosis, it is extremely difficult to evaluate the effect of an antimicrobial agent upon tuberculous processes which are chiefly limited to the lung. The course of pulmonary tuberculosis is variable, and there is no certain method by which to predict the degree of resistance which may be displayed by an individual patient.

Speedy and extensive resolution even of large and well-established exudative lesions occasionally occurs on a regimen of bed rest. Thus, in an individual patient, it is not possible to relate with certainty an unusually rapid resolution to the administration of an antimicrobial agent. More convincing evidence that there is a causal relationship between the drug and healing is the demonstration that regressive changes appear *with regularity* after it is administered. In the 43 patients with pulmonary tuberculosis in the present study, the institution of streptomycin therapy was followed in every instance by a measurable degree of clinical, roentgenologic or bacteriologic improvement in the status of the infection. The degree of improvement was only slight or temporary in some instances, whereas in others it was considerable and sustained. There were no cases treated, however, in which improvement of some degree failed to occur.

Extensive resolution and an appreciable reduction in cavity size during streptomycin therapy was observed in 15 of 18 patients with predominantly exudative pulmonary tuberculosis of moderately advanced or far advanced extent. In nine of the group, the improvement continued to the point of cavity closure and reversal of infectiousness during or shortly after the period of antimicrobial therapy. A similarly satisfactory status was attained by another five patients when the streptomycin treatment was followed by appropriate collapse therapy. All of the latter group had been considered unsuitable subjects for collapse therapy at the time antimicrobial therapy was started. Less striking changes were observed after streptomycin therapy in 18 patients with fibro-cavernous disease of long standing. Even among this group, however, cavity closure and sputum conversion occurred in four instances, retrogressive changes were observed in most of the others, and complete healing occurred in all of eight cases of laryngeal or tracheobronchial disease.

Thus on the basis of the regularity with which improvement occurred after the administration of streptomycin, it would seem that the beneficial results noted in this series of 43 patients with pulmonary tuberculosis were definitely attributable to the drug therapy.

In tuberculosis, as in other infections, healing presumably proceeds by essentially the same mechanisms whether the inhibition of the infection

results from antimicrobial therapy or is accomplished by the natural defenses of the host. Thus it would not be anticipated that the results attainable by the streptomycin therapy of pulmonary tuberculosis would be significantly superior to the most successful results ever observed previously in the natural healing of the disease. The principal effect of chemotherapy should be to produce a material increase in the number of such successful results and possibly to shorten the average time required for their accomplishment.

Recently developed tuberculous lesions may differ widely in character from a predominantly exudative to a predominantly proliferative process. In either type of lesion, the speed with which a significant degree of necrosis may occur, varies considerably. In general, however, the extent of tissue necrosis bears a relationship to the duration of the lesion. It would seem that the degree to which a particular lesion would be reversible by antimicrobial therapy (or by the natural forces of immunity) is largely determined by the amount of necrosis which had already occurred when the progress of the infection had been halted.

In extensive studies of the natural healing of exudative lesions, Amberson [7] has noted that a virtually complete resolution of the outer zone of the lesion may occur. Resolution does not occur, however, in the central and oldest portion of the lesion which is almost invariably necrotic by the time the total lesion is first detectable. The subsequent course of the infection thus depends to a large extent upon the size and the ultimate fate of the necrotic residue. It may be discharged through a bronchus, thus leaving a residual cavity which, if sufficiently small, may heal promptly. In other instances, the residual lesion may be encircled by fibrous tissue and eventually calcified in whole or in part. In either event, a focus of infection, which may even be undetectable roentgenologically, persists for a period measurable in years after the complete resolution of what was perhaps the major portion of the lesion.

In the present investigation, the course of the predominantly exudative lesions under streptomycin therapy has followed the exact sequence of events described by Amberson for the corresponding stages in the natural resolution of such lesions. In most instances, areas of pneumonia of variable size have contracted to a large degree leaving a residual core of consolidated lung or a constricted or apparently closed cavity. In other pneumonias in which the areas of caseation apparently represented a major portion of the total lesion, many large areas of excavation appeared during antimicrobial therapy. It is probable that the subsequent behavior of the residual lesions will be much the same as occurs under comparable conditions in the natural history of the disease.

It is not possible at this time to estimate the degree of reversibility of recently developed proliferative lesions because of the well recognized difficulty in distinguishing them from the exudative type of process during life. From the histopathologic observations in streptomycin-treated generalized hematogenous tuberculosis [1] and from experiments in guinea pigs,[6] it seems

likely that proliferative lesions are reversible to a considerable degree. Presumably in this type of lesion also, the extent of the necrosis present before antimicrobial therapy is the factor which determines the maximal attainable result.

It is not surprising that only a slight degree of improvement was observed in most of the streptomycin-treated patients who had chronic disease with established secondary fibrotic changes. In this stage of tuberculosis, the anatomic changes resulting from the reparative process itself constitute a barrier to the further healing of the lesions. Cavities are lined by walls of fibro-caseous tissue, often of considerable thickness. The lower ramifications of the bronchial tree may be so distorted or destroyed that proper drainage of areas of indolent caseating disease is not possible. Areas of recently developed disease may also be present as extensions of the chronic process. From the observations in the present study, it would seem that such areas of new involvement usually recede under antimicrobial therapy, but the underlying disease remains essentially unaffected.

In addition to the factors of tissue destruction and consequent anatomic distortions, there are other properties of tuberculous lesions which might condition the effectiveness of streptomycin. A most important question in this connection is whether the bacilli have unimpeded access to the drug in all types of pulmonary lesions.

It is probable that the actual physical penetration of the lesion by the drug is accomplished in virtually all instances. It has been demonstrated [8] that proliferative and fibro-caseous tubercles are readily penetrated by a variety of colloidal dyes and sulfones. As streptomycin, in the dosages in general use, is apparently freely distributed throughout the extracellular fluid of the body (central nervous system excepted),[9] it is reasonable to assume that it penetrates all viable inflammatory tissue in the lung including the walls of tubercles. Moreover, the high incidence of the appearance of streptomycin-resistant strains of tubercle bacilli in patients with chronic cavities suggests that the organisms within the lumen of the cavity have been in contact with the drug.

Even though physical penetration of all lesions presumably occurs, however, the particular type of lesions present might exert a considerable influence on the activity of the drug. It is known that the antimicrobial activity of streptomycin may be appreciably reduced by reduction in the pH of the environment to below 6.0.[10] If the pH of the exudative tuberculous lesion is essentially the same as in other pneumonic exudates (pH 6.7 to 7.1),[11] it would be in a range of high streptomycin activity. In contrast, a large area of tuberculous caseation would be considerably more acid. Moreover, such a large area of caseation might conceivably hinder diffusion and otherwise interfere with the activity of the drug. It should be noted that these possible effects of a large area of caseation on drug activity should also operate to interfere with the natural defenses of the host.

The relative importance of intracellular and extracellular bacilli in the

intensity of the infection and their respective vulnerability to the drug are fundamental questions in consideration of streptomycin activity at the site of the lesion. It is well recognized that many of the bacilli in a tuberculous lesion are situated within the monocytes. Information is limited concerning the relative proportions of intracellular and extracellular organisms in the various types of lesions. It is probable, however, that extracellular proliferation of bacilli is most prominent in the rapidly progressing lesions. These extracellular organisms should have easy access to streptomycin. In contrast, it is not known whether the bacilli within the monocytes can be reached by the drug. If the drug does not have access to the organisms its field of action would be limited to the bacilli multiplying extracellularly and such organisms as are freed from disrupted monocytes. It is conceivable, therefore, that the principal action of streptomycin consists of an interference with the proliferation of the extracellular component of the infecting population and that the phenomena of "crisis" and rapid resolution are direct consequences of such an action. A change in the host-parasite relationship of this general type may represent the maximal effect attainable from the use of this antimicrobial agent.

The possible relationship between a sudden inhibition of bacterial multiplication and the appearance of abrupt defervescence was discussed in a previous communication.[1] The same phenomenon of "crisis" which was observed in generalized hematogenous infections, also occurred in certain of the patients with acutely progressive exudative lesions in the lung (figure 5a).

The important influence of the nature of the lesion on the results attainable from the use of streptomycin is by no means unique to the antimicrobial therapy of tuberculosis. For example, the nature of the lesion plays an important rôle in determining the different end results usually observed after the antimicrobial therapy of the pulmonary infection caused by *Pneumococcus* and that produced by *Klebsiella*. Agents are available (sulfadiazine, penicillin, streptomycin) which are highly active on one or both of these two bacterial species both in vitro and in vivo. In pneumococcus pneumonia, the destruction of lung tissue is negligible, and powerful defenses are available or can be readily mobilized for the maintenance of a drug-induced remission. As a consequence, the administration of antimicrobial therapy at any stage of the disease short of terminal respiratory or vascular failure is usually followed by prompt recovery with restitution of the pulmonary tissues to their pre-disease state. In contrast, in Klebsiella pneumonia it is not usually possible to attain such a satisfactory result when antimicrobial therapy is started subsequent to the first few days of the acute infection. In this infection, a considerable destruction of lung tissue may occur rapidly, sometimes within 24 or 48 hours of onset. Once a significant degree of destruction has occurred, the subsequent control of the infection either by the defenses of the host or by antimicrobial therapy usually results in a chronic disease with a variable degree of pulmonary damage.

The relative importance of a drug which is antimicrobic in vivo, in the treatment of a particular infectious disease, is conditioned not only by the nature of the lesions but also by the speed with which a significant degree of resistance can be mobilized by the host. Obviously, it is this latter factor which determines the ideal length of the period during which chemotherapy should be administered. Thus far, even in the most successful of the streptomycin-treated cases of pulmonary tuberculosis, the arrest of the infection presumably was not accompanied by an eradication of tubercle bacilli from the lungs. Moreover, it is not to be anticipated, except under the most unusual circumstances, that such a total eradication of bacilli would occur during or immediately after streptomycin therapy. Aside from the questions of resistant strains of bacilli or the toxicity of the drug, it would obviously not be practicable to administer streptomycin for the period of years during which tubercle bacilli may persist in arrested lesions. Thus the success of streptomycin therapy rests on the ability of the patient to control the infection after the administration of the drug has been discontinued.

At present, there is no way in which the status of host resistance, or more precisely, the host-parasite relationship, can be accurately evaluated other than by observation of the outcome of the infection. It is known that certain individuals have shown evidence of the operation of impressive forces of resistance during the several months after the appearance of relatively extensive exudative-type lesions. There is no information, however, as to whether such rapidly operative resistance is an exceptionally rare phenomenon or whether it would be as quickly evident in most patients if the progress of the infection were reversed by antimicrobial therapy. In the present small series, the appearance of relapse while still on bed rest in two patients who had attained remissions during streptomycin therapy, is evidence that in some instances several months of streptomycin therapy are insufficient to ensure sustained control of the infection. Conversely, considerable hope is afforded by the fact that relapse has not occurred during the period of observation in the majority of streptomycin-treated pulmonary infections which have attained remission, both in the present study and in that of Hinshaw and Feldman. Moreover, in several of our patients extensive roentgenologic clearing with reversal of infectiousness occurred during the four to eight weeks after the cessation of streptomycin therapy. As most of these infections were actively progressing at the time antimicrobial therapy was started, it would seem that they represent examples of the ready operation of host resistance once the progression of the infection has been artificially checked.

It should be noted that, with the exception of an initial infection with *M. tuberculosis,* it is not definitely established that an important degree of host resistance actually *develops* during the months or years after the appearance of a progressive pulmonary lesion. The possibility exists that the observed phenomena of host resistance (or change in the balance of host-parasite relationship) do not develop, but are merely revealed, when

the onward progress of the infection has been suddenly checked by chemotherapy. In either event, however, it is likely that the chance for the maximum effectiveness of the host-defenses would be considerably enhanced the longer they were free to operate against an artificially inhibited infection.

Thus, from a consideration of both the nature of tuberculous lesions and the poorly understood variables of the host-parasite relationship, it is apparent that the ideal procedure in the chemotherapy of tuberculosis would be to administer the drug for many months.

In the present study, the administration of streptomycin for periods of three to four months to patients who continued to discharge *M. tuberculosis* was accompanied in all but one instance by the appearance of organisms which were highly resistant to streptomycin in vitro. In a previously reported study [1] of the streptomycin treatment of generalized hematogenous tuberculosis, it was observed that, under the conditions of the test as employed in this laboratory, the appearance of bacilli which were drug-resistant in vitro indicated the presence of streptomycin-resistant infections in vivo.

Unlike generalized hematogenous tuberculosis, it would not be anticipated that relapse would inevitably occur in pulmonary tuberculosis merely because of the appearance of drug-resistant bacilli. Improvement continued in four patients of the present study after drug-resistant organisms were isolated, and sputum conversion occurred despite the development of resistance. In those instances, however, the extent and rapidity of the initial improvement had been most noteworthy or the cavitary source of possible new bronchiogenic disseminations had been obliterated by collapse therapy.

Another factor which makes correlation of in vitro and in vivo bacterial sensitivity difficult in pulmonary tuberculosis is the phenomenon of delayed roentgenologic clearing mentioned previously. During the third and fourth months after the start of streptomycin therapy, extensive roentgenologic clearing may occur even though the administration of the drug is discontinued on the forty-second day of treatment. If such delayed roentgenologic clearing appeared in a patient in whom chemotherapy had been continued, it might easily be assumed that the improvement was related to the continued administration of the drug. Moreover, if such a patient were discharging streptomycin-resistant bacilli during the last one or two months of therapy, it would be easy to arrive at the false conclusion that the infection was still streptomycin-sensitive in vivo.

In the present study there were only seven patients who continued to discharge bacilli throughout and subsequent to the streptomycin treatment. All of them had shown definite evidence of some regression of the infection during the first weeks of streptomycin therapy at a time when their organisms were highly sensitive to the drug in vitro. At a variable interval after the first detection of drug-resistant bacilli, the tuberculous infections again became actively progressive. In every instance, the newly progressive infections were completely uninfluenced by the further administration of streptomycin and four of these patients have died.

It would seem, therefore, in pulmonary tuberculosis, as in generalized hematogenous tuberculosis, that the discharge of bacilli which are streptomycin-resistant in vitro, indicates the presence of a drug-resistant infection in vivo. The only difference in the significance of the phenomenon in the two types of infection is that relapse does not necessarily follow its appearance in pulmonary tuberculosis. It also appears that the incidence of bacterial resistance is directly related to the duration of therapy. In both types of tuberculosis streptomycin-resistant tubercle bacilli appeared in the great majority of patients from whom organisms could be obtained after three months of streptomycin therapy. Moreover, in some individuals the appearance of drug-resistant organisms was detected as early as the second month of chemotherapy. On the basis of these observations, it appears that the period during which streptomycin exerts antimicrobial activity in tuberculosis terminates in most infections some time between the sixtieth and the ninetieth days of therapy. Thus the range of the period during which the administration of streptomycin serves a useful purpose is sharply limited.

As pulmonary tuberculosis treated by any method has a pronounced tendency toward relapse, it is advisable to attempt to avoid the emergence of strains of tubercle bacilli which are predominantly streptomycin resistant. One method by which this might be accomplished would be to administer the drug for a total period of two months or less. On the basis of preliminary experience, it would seem that with the 42 day regimen in use in this study, the incidence of streptomycin-resistance is drastically lowered but that its development is by no means completely eliminated. There has not been sufficient experience as yet with the one gram daily dose of streptomycin to determine whether the incidence of bacterial resistance is related to the size of the daily dose as well as to the duration of treatment. Moreover, there has been no opportunity to observe the incidence of bacterial resistance in patients who have received two 42 days' courses of streptomycin separated by an interval of several months.

*Value of Streptomycin in Pulmonary Tuberculosis.* Although the greatest value of streptomycin is clearly in relatively acute processes which can be materially influenced by a relatively short period of antimicrobial therapy, the drug is of important though limited value in certain cases of chronic tuberculosis. In a few instances, notably in slowly progressive chronic lesions which are presumed to be chiefly proliferative, marked regression may take place during or shortly after the completion of streptomycin therapy. The principal value of the drug in chronic tuberculosis, however, will probably be in the treatment of laryngeal and tracheo-bronchial complications and as an adjunct to surgical therapy.

Tuberculous involvement of the larynx or bronchi usually represents a potentially serious complication of pulmonary tuberculosis. Without antimicrobial therapy, the ulcerative lesions of these structures have a tendency toward slow progression. Although natural healing occurs, it is slow and uncertain. Moreover, because the spontaneous healing of tracheo-bronchial

lesions is always protracted, the resulting distortion of the airway may considerably complicate the underlying pulmonary infection. Thus the rapid healing of laryngeal and tracheobronchial tuberculosis which has been observed almost uniformly after the administration of streptomycin, represents a notable advance in tuberculosis therapy. It must be appreciated, however, that, unless the underlying pulmonary tuberculosis is also controlled, the laryngeal or tracheobronchial disease is likely to recur with drug-resistant organisms.

The introduction of an antimicrobial agent effective against *M. tuberculosis* inevitably enlarges the number of cases in which surgical therapy is feasible. It is probable that the principal use of streptomycin in the treatment of chronic fibrocavernous tuberculosis will be as an adjuvant to surgery. In any form of tuberculosis, however, the frequency with which drug-resistant strains of tubercle bacilli appear is such that the administration of streptomycin will evidently have to be properly timed in relation to the planned operative procedures. Retrospectively it is apparent that in some of the cases in the present study opportunities were missed for surgical treatment. This was true particularly among those treated early in the study before the correlation between the appearance of drug resistance and loss of therapeutic effectiveness was evident. Later, in several cases whose initial improvement was considerable, yet apparently had not sufficient momentum to attain a satisfactory remission without mechanical measures, thoracoplasties were performed within 12 to 16 weeks after the start of antimicrobial therapy. The results were encouraging in these few instances, considering especially the character of the original disease. It is possible that in some situations, in which the necessity for surgical collapse is clearly apparent from the start, the best results will be obtained by operating early in the course of streptomycin. On the other hand, there are no certain criteria for predicting, at any time prior to a reversal of the favorable trend, the ultimate improvement which may follow streptomycin. Reference has already been made to a few cases in which with only slight early improvement the total regression after several months was unexpectedly satisfactory. The time at which the patient's condition is optimal for necessary surgery can, therefore, not always be easily determined.

Another field in which streptomycin may be useful in conjunction with surgery is as a prophylactic agent against the extensions of the disease which occasionally occur as a complication of thoracoplasty. A large scale investigation of this type of regimen is in progress in the Veterans' Administration.[12]

At the present time it would seem proper to administer streptomycin to cases of progressing moderately advanced or far advanced pulmonary tuberculosis of recent origin and in which the disease is of predominantly exudative character. In chronic cases, in which extensive fibrotic changes have already occurred, streptomycin should not be used until the timing of its administration has been carefully considered in relation to possible sur-

gical therapy. Otherwise, the usual result will be merely the emergence of a drug-resistant strain of organisms in a patient who has attained only a short-lived period of improvement. It also seems proper to administer streptomycin to patients with ulcerating laryngeal or tracheo-bronchial tuberculosis. Occasionally with such involvement the underlying pulmonary process is so extensive that arrest by any combination of therapeutic measures seems highly unlikely. In this situation, it may be advisable to administer the streptomycin in short (two week) courses in an attempt to obtain symptomatic relief while avoiding the appearance of bacterial resistance.

Because of neurotoxicity, streptomycin should not be used in the treatment of patients with pulmonary tuberculosis of minimal extent, or in patients with more advanced disease in which the outlook is favorable with conventional methods alone. Even if it should be established that satisfactory therapeutic efficiency and a low incidence of neurotoxicity occur when the total daily dose of streptomycin is limited to only one gram, the problem of drug-resistance remains a deterrent to the unrestricted use of this antimicrobial agent. There is no indication that arrest of tuberculosis accomplished with the aid of streptomycin is free of liability of relapse, any more than arrest resulting from spontaneous healing. To use the drug unnecessarily, even though the immediate result be good, may amount to wasting a therapeutic resource for which there is possibility of later need.

## Summary

The administration of streptomycin for periods of 42 to 120 days to 43 patients with pulmonary tuberculosis was followed, in every instance, by some degree of measurable improvement in the status of the disease. Of 18 patients, followed six weeks or longer after treatment, whose pulmonary lesions were predominantly exudative in nature, nine attained satisfactory early remissions during or shortly after the cessation of the antimicrobial therapy. Of these, two relapsed within six months, requiring collapse therapy, and a third relapsed within 12 months. Another six patients showed considerable improvement under streptomycin therapy, but fell short of attaining full remission. The suitability of these cases for collapse therapy, however, was appreciably enhanced and this was subsequently undertaken in five with apparent success. In three patients there was no significant benefit and a short period of symptomatic improvement was followed by early resumption of the progressive course of the infection.

Less striking changes were observed in another 18 patients, also followed six weeks or longer, with chronic fibrocavernous disease. Four had fully satisfactory early responses and four more attained favorable results when the antimicrobial therapy was followed by thoracoplasty. In 10 of the 18 cases there was a short period of temporary improvement but no lasting benefit. Strains of tubercle bacilli which were highly resistant to the action of streptomycin in vitro were obtained from 10 of 11 patients who continued

to discharge bacilli during 75 to 120 days of chemotherapy. The incidence of drug-resistant strains of bacilli was much lower when streptomycin therapy was continued for only 42 days. In every instance in which relapse occurred after the appearance of streptomycin-resistant organisms, the course of the infection was completely uninfluenced by the further administration of streptomycin.

## Conclusions

1. The administration of streptomycin to patients with pulmonary tuberculosis is followed by a definite effect upon the course of the infection. The magnitude and the durability of the effect depend upon the nature of the lesion, the status of the host-parasite relationship, and the length of time the infecting organisms remain streptomycin-sensitive.

2. In pulmonary tuberculosis, as in generalized hematogenous tuberculosis, the appearance of streptomycin-resistant organisms (under the conditions of the test employed) indicates the presence of an infection which is drug-resistant in vivo.

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# CASE REPORTS

## CHRONIC PORPHYRIA *

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The clinical picture and criteria for the diagnosis of porphyria, congenital or acute, have been adequately discussed in the recent literature. The rarity of the disease and the failure of many physicians to be acquainted with it are factors undoubtedly causing many cases to be overlooked at the present time. We are reporting this case because of its chronicity, a point which is not emphasized in most discussions, and because of the presence of extreme pigmentation and definite neurological involvement.

### Case Report

Mrs. D. B., a 44 year old white housewife, was first admitted to the Albany Hospital on February 4, 1945 with the complaints of vaginal bleeding; frequent, painful urination; and occasional inability to void, of several months' duration. Previous to the onset of the present illness she had always enjoyed good health with the exception of three miscarriages prior to the birth of her son, now 14 years old. Following this delivery, she and her family noted that her skin was turning dark, but not being otherwise inconvenienced, she did not seek medical advice. She stated that for the last few years she had had spells of crying and nervous tension.

Physical examination on this admission revealed a woman who looked older than the stated age and whose skin was heavily pigmented, especially the nose and cheeks. Pelvic examination showed an irregularly enlarged uterus but the remainder of the physical examination was not remarkable. Routine urine and blood studies were normal. On the second hospital day, a pan-hysterectomy, right salpingo-oöphorectomy and appendectomy were performed with removal of a fibroid uterus. Post-operatively, her course was marked by almost daily attacks of nausea and vomiting for 15 days. A urine examination during this time was noted to be mahogany-colored and the nurses' notes report the urine to be very dark reddish-brown on another occasion. She was discharged on the nineteenth hospital day to the care of her family physician.

At home, she was confined to bed, being extremely weak, scarcely able to lift her arms or legs. Her appetite was very poor and she vomited frequently but had no abdominal pain, constipation, diarrhea or urinary difficulties. She was treated by her doctor with parenteral liver extract and adrenal cortical extract but failed to show any improvement. Because of lack of response to the adrenal cortical extract, a blood pressure of 140 to 160 mm. Hg systolic and 100 to 120 mm. diastolic, and persistence of dark-colored urine, the tentative diagnosis of Addison's disease was doubted and the patient returned to the hospital for further study.

*Second Hospital Admission* (March 25, 1945). The chief complaints on admission were extreme weakness of arms, legs and neck; recurrent nausea and vomiting; weight loss of 30 pounds since the previous hospitalization.

*Family History.* The family history was non-contributory. There were eight siblings living and well.

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From the Department of Medicine, Albany Hospital, Albany, N. Y.

*Past History.* Previous to the present illness there was no history of abdominal pain, nausea, vomiting, weakness or dark-colored urine. The patient had not been taking drugs of any kind and there had been no known exposure to lead or to arsenic.

*Physical Examination.* Temperature 99.0°; pulse 128; respirations 32. As on the previous admission, the patient appeared much older than the stated age. Her skin was deeply pigmented over the whole body but especially over the face where the nose and malar eminences were actually black (figure 1). There was moderate hypertrichosis over the lateral frontal areas. The pupils were round, regular and equal; they reacted to light and accommodation. There was no nystagmus. The upper incisor teeth were brownish in color and protuberant. There was no abnormal pigmentation of the mucous membrane of the mouth except for a single, small, dark brown spot 4 mm. in diameter on the lower lip. The neck muscles were weak. The

FIG. 1. Appearance of patient contrasted with that of a normal young adult. Note generalized pigmentation of skin with concentration over nose and cheeks; the prominent brownish-colored incisor teeth. The hypertrichosis over the lateral frontal areas is not clearly shown.

thyroid was not palpable. The lungs were normal to percussion and auscultation. The heart was not enlarged to percussion; the rate was rapid with normal rhythm; there were no thrills or murmurs. The blood pressure was 160 mm. Hg systolic and 100 mm. diastolic. The abdomen presented a well-healed midline, operative scar; no organs or masses were palpable.

The tissues of the abdomen showed considerable weight loss and there was marked wasting of the extremities and atrophy of all muscles but especially of the interossei and of the thenar eminence of the right hand and of the left gastrocnemius. There was generalized weakness of all extremities with a foot drop on the left. The reflexes were as follows: the triceps and biceps were weak but obtainable; the radial, abdominal, knee and ankle reflexes were absent. No pathological reflexes were present. There was no astereognosis and the proprioceptive reflexes were intact. Perception to pinprick was diminished over the distribution of the right ulnar nerve and increased over the course of the left peroneal nerve.

*Laboratory Data.* The urine was reddish-brown in color; sugar 1+. The total coproporphyrin in a 24-hour urine specimen of 565 c.c. was 407 gamma (normal

values are under 100 gamma). Nearly all of this excess of porphyrin was the type III isomer so that the findings are qualitatively and quantitatively abnormal. There was no uroporphyrin and the porphobilinogen test was likewise negative.* Hemoglobin 12.0 gm.; red blood cells 4,000,000 per cu. mm.; white blood cells 8,000 per cu. mm. The differential count was essentially normal. Blood Wassermann negative. Non-protein nitrogen 53 mg. per cent; uric acid 7.0 mg. per cent; icteric index 13; serum bilirubin 1.3 mg. per cent; serum proteins 6.2 gm. per cent with albumin 2.8 gm. per cent and globulin 3.4 gm. per cent. Glucose tolerance test showed fasting blood sugar of 101 mg. per cent; ½ hour: 209 mg. per cent; 1 hour: 229 mg. per cent; 2 hours: 197 mg. per cent. Serum sodium 429.3 mg. per cent; serum potassium 30.6 mg. per cent and serum chlorides 420 mg. per cent.

A chest roentgen-ray showed a small, discrete nodular area at the right lung base with some fibrosis just above the diaphragm, interpreted as some former inflammatory change, or a possible metastatic nodule. The cardiac shadow was normal in size. A flat plate of the abdomen revealed a ring-like shadow in the region of the gall-bladder, but no visible calcification in either adrenal gland. An electrocardiogram showed a normal sinus rhythm with a rate of 118. AV, QRS and ST times were normal. $ST_{1 \text{ and } 2}$ were slightly depressed; $T_1$ low; $T_2$ diphasic; $R_3$ low and slurred; $T_3$ inverted. The changes in the ST lines and T-waves were believed possibly due to fatigue from the rapid rate. Biopsy of the skin from the abdomen showed an iron-free pigment disposed in normal fashion in the lowest layer of the epidermis.

*Course.* While in the hospital, the patient showed very little change in the neurological findings. Emotional instability was not noted, and symptoms of bulbar involvement did not appear. Nausea and vomiting occurred on two or three occasions during the first few hospital days, clearing spontaneously thereafter. Parenteral vitamins were administered daily. She was discharged on the twelfth hospital day to be followed by her local physician.

## Discussion

It has been customary to classify porphyria as either congenital, acute or chronic.[1] In congenital porphyria, the onset is usually in males in infancy or early childhood; there is great sensitivity to light and uroporphyrin type I is usually excreted in large amounts in the urine. In the acute form, the onset is usually in females in the third to fifth decades, there is little or no light sensitivity and uroporphyrin type III is found in the urine in excessive amounts. Intermediate is a group which has been called "chronic porphyria" where either a type I or III uroporphyrin or coproporphyrin is excreted. The skin is somewhat sensitive to light and symptoms referable to the gastrointestinal tract are present.

The problem of porphyria may be regarded as an "inborn error of metabolism" and probably not limited only to the stage of acute symptoms.[2] There are two porphyrins that are important in cases of porphyria, uroporphyrin which is found in small amounts in normal urine, and coproporphyrin which is found in small amounts in normal feces. Only two isomer types, namely I and III, of these porphyrins occur in nature. One of the most reasonable theories as to the pathogenesis of the disease is that during the formation of hemoglobin, the metabolism of porphyrin remains at an embryonic level.[3] Although the disease is a chronic metabolic disorder and it has been shown that uroporphyrin may be excreted by patients between attacks,[4, 5, 3] the cause of the acute attacks is not definitely known.

* We are greatly indebted to Dr. C. J. Watson of the Medical School of the University of Minnesota who was kind enough to make the analysis for porphyrin in the urine.

Since the opportunity to observe a patient with porphyria is not often presented, we would like to point out briefly the important features in the clinical types.

Congenital porphyria is frequently familial.[3, 6] Only one case of apparent hereditary transmission (father to son) has been observed (Radaeli, cited by Mason et al.[3]). Turner and Obermayer [7] reviewed the literature up to January 1939 and found 86 cases of congenital porphyria with nine possible exceptions recorded. There were 56 males and 26 females in the series. The onset occurred in the first 10 years of life in 36 cases and in the majority of the remainder before 40 years of age. One case occurred in the sixth decade and another in the seventh decade. A familial incidence was recorded in 30 instances.

With rare exceptions, the earliest and most important sign is red urine.[3] This may precede the skin changes by weeks or years.[6] The excretion of colored urine may be intermittent or continuous. Attention may be called to the disease by the development of skin lesions on exposure to sunlight. Although this sensitivity to light is usually apparent in the early years of life, it may not appear until late. One of Gunther's patients showed no signs of photosensitivity until the fiftieth year.[3] The skin lesions have been described under the names "hydroa vacciniforme" or "hydroa aestivale" but not all of the reported cases of hydroa aestivale have exhibited porphyria. After exposure to sunlight, the skin eruption usually begins with a diffuse erythema followed by edema. A vesicular or bullous eruption may follow and if secondary infection occurs, pustules develop. Healing is accompanied by scarring and deformity. The scars usually become pigmented. When exposures are frequent, the finger tips, nose and ears may become deformed. Contracture of scar tissue may bring the upper teeth into view (figure 1). Generalized pigmentation of the skin is common and is frequently accompanied by hypertrichosis.[6, 7] The pigment is probably porphyrin. It has been found in the bones and teeth of patients who died from chronic porphyria.[3] The pigmentation differs from that seen in Addison's disease in that the mucous membranes are not involved.[5]

Up to 1939, over 250 cases of acute porphyria had been reported.[1] About 100 cases were classified as acute, toxic and 153 as acute, idiopathic porphyria.[7] These types are not distinguishable by clinical or laboratory methods and are classified as toxic if a noxious agent can be identified. Mason and his associates [3] found a barbiturate was the usual toxic agent since they showed that out of 100 cases, sulfonal was used in 68 and trional in 11. Veronal, lead, acetanilid and nitrobenzol are also stated to be associated with acute porphyria. However, they may be only precipitating factors. Acute porphyria may also be a congenital disorder for instances have been described where one member of a family had acute porphyria while another had the congenital type. It has been observed in three generations and is inherited as a Mendelian dominant.[1]

Turner [4] has shown that porphyria may be a persistence of a fetal pyrrol metabolism. He states that the metabolic fault is not limited to the period of acute symptoms and claims that acute idiopathic porphyria may be as much an inborn error of pyrrol metabolism as is congenital porphyria.

The idiopathic type has occurred as isolated instances although there is one exception, a family with three sisters, mother and grandmother.[8]

The acute attack is often preceded by an interval of general malaise with vague intestinal complaints, insomnia, nervousness and weakness as the chief symptoms.

The acute attack begins with abdominal pain which is colicky and severe. Nausea and vomiting are usually present. Of importance in differentiating these findings from an acute surgical abdomen is the lack of muscle spasm. Constipation is common. Roentgen-rays of the intestinal tract may show marked spasm of the ileum, while the stomach and colon may be dilated,[6] though there are exceptions to this. Chandler and his associates [9] report a patient with acute, idiopathic porphyria who had severe, cramp-like abdominal pain. Vomiting was frequent. A hard mass was palpable in the epigastrium. The clinical picture was one of a malignant growth but at operation the stomach was found to be in a state of extreme contraction producing the apparent tumor. There may be a fever of 100° to 102° and a leukocytosis of 15,000 to 20,000. The urine at this time is dark brown or reddish and porphyrin, or rarely the colorless porphyrinogen, is present.[3]

About one-half of the patients with acute toxic or idiopathic porphyria die of involvement of the central nervous system in an ascending or Landry type of paralysis.[6] Sensory disturbances, as hypesthesia and paresthesia, may be present. Hallucinations and delirium as well as apathy is seen.

Usually patients with acute porphyria excrete large amounts of uroporphyrin III and I in the urine with a great preponderance of the type III isomer. Usually only a small amount of coproporphyrin III is present in the urine.[10] There are, however, clear cut exceptions to this.[2] Fischer and Libowitzky [11] reported the first case of acute toxic porphyria with the excretion of uroporphyrin I, and Turner [4] reported the first case of the idiopathic type where this porphyrin was found.

Our patient is somewhat difficult to classify. This case is unusual in that deep pigmentation is present in conjunction with neurological involvement and coproporphyrin III was isolated from the urine. Sensitivity to light has not been observed in acute porphyria [3] but is found in the congenital type. On the other hand, symptoms referable to the central nervous system occur in many patients with acute porphyria.[6] Uroporphyrin, type I or III, is found in excessive amounts in congenital and acute porphyria, respectively. Coproporphyrin is found in large quantities in the urine of patients with many forms of hepatic disease,[12] including atrophic cirrhosis, infectious jaundice, obstructive jaundice and hemochromatosis. Our patient did not have any clinically demonstrable liver disease.

Dobriner and Rhoads [1] discuss a group of cases of porphyria which are classified as chronic. According to them, this term was first applied by Gunther to cases with increased excretion of porphyrin, which could not be called either congenital or acute. The skin is somewhat sensitive to light and symptoms arising from the intestinal tract are present. Coproporphyrin III has been found in the urine, alone [13] and in combination with uroporphyrin I and III.[1]

Taylor and his associates [14] recently observed a woman with chronic porphyria exhibiting photosensitivity with abdominal pain, nausea and vomiting. Large amounts of coproporphyrin I and III were excreted in the urine for a period of over one year.

Our patient seems to fit in this classification. The late onset at age 34 and the duration over a period of 14 years are significant. The isolation of such large amounts of coproporphyrin III from the urine is uncommon in the absence of liver disease and excludes the diagnosis of acute or congenital porphyria.

One year after discharge from the hospital, a follow-up report was received from the patient's doctor who stated that she is gradually getting stronger. She can walk and feed herself and is able to work one-half a day at light housework. The pigmentation does not seem to be as dark. The reflexes are unchanged. There has been no abdominal pain, nausea or vomiting. Treatment has consisted of the administration of liver extract, vitamin B and iron.

## Summary

An unusual case of chronic porphyria is presented, featuring striking, deep pigmentation of the skin, neurological changes and gastrointestinal symptoms. Coproporphyrin III was isolated from the urine. A brief review of the literature is included.

The authors are indebted to Dr. Thomas Ordway for permission to study this patient and for helpful criticism of the manuscript.

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# ACUTE HEMOLYTIC ANEMIA WITH AUTO-AGGLUTINATION FOLLOWING SULFONAMIDE THERAPY *

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THE following case is reported because it represents a rare phenomenon previously described as a complication of sulfonamide therapy and as a potential source of error in blood typing.

A 23 year old soldier was admitted on January 7, 1945 with a gunshot wound through the left abdomen. Laparotomy revealed transsection of the jejunum in two places and a perforation of the stomach. The exit wound was in the left lumbar region. The perforations of the stomach were sutured, the involved jejunum resected, and an end-to-end anastomosis done. Approximately 2,000 c.c. of blood were found in the peritoneal cavity. Four grams of sulfanilamide powder were placed into the peritoneal cavity, another four grams into the retroperitoneal space. Severe shock necessitated four transfusions, each of 500 c.c. of type "A" blood, and 750 c.c. of plasma on the day of admission. Cross matching with the donor's blood showed compatibility. There was no transfusion reaction.

On January 8 five grams of sodium sulfadiazine were given intravenously in conjunction with 3,000 c.c. of saline and one unit of plasma. Penicillin therapy was instituted, using 20,000 units every two hours. The patient's temperature ranged from 101 to 103° F. The blood count showed: Hemoglobin 85 per cent; erythrocytes 5,180,000. Leukocyte count was 6,000 with 65 per cent neutrophiles and 35 per cent lymphocytes. The blood sulfanilamide level was 3.1 mg. per cent.

On January 9 the sulfonamide medication was discontinued because of a drop of the leukocyte count to 5,000. The sulfadiazine level was 9.2 mg. per cent. Penicillin, plasma and intravenous fluids were continued.

On January 10 a left pleural effusion developed, accompanied by a rise of temperature to 105°.

On January 13 the erythrocyte count had dropped to 2,750,000, the hemoglobin to 60 per cent. The leukocyte count was 7,200 with 67 per cent granulocytes and 33 per cent lymphocytes. Five hundred c.c. of type "A" blood were transfused without reaction.

A roentgenogram taken on January 15 showed decrease of the pleural effusion.

On January 18 an infected intraperitoneal hematoma was incised and drained. The erythrocyte count was 2,200,000, hemoglobin 50 per cent, the leukocyte count 7,000 with 68 per cent granulocytes. On this day jaundice was first noticed. The icteric index was 37.

Another transfusion was indicated. Cross-matching with type "A" blood from four different donors (slide technic at room temperature) showed agglutination only on the minor side (donor's serum with recipient's cells). Retyping the patient's cells with the standard rabbit antiserum now showed an apparent "AB" type. On cross matching, however, with several "AB" bloods there was incompatibility on the major and minor side. It was then found that the patient's serum agglutinated his *own* cells. This finding suggested the possibility of this being a case of hemolytic anemia with "cold" auto-agglutination as described by Antopol and his associates.[1] Retyping the blood at 37° showed type "A," no cross agglutination with other type "A" bloods, and no auto-agglutination.

Further relevant laboratory data obtained on January 19 were the following: Erythrocyte fragility: slightly decreased. Van den Bergh test: biphasic reaction.

* Received for publication July 11, 1946.

Serum bilirubin: 7.5 mg. per cent. Blood culture: negative. The urine contained 3 plus albumin, increased urobilinogen (1:64), but no hemoglobin.

During the following 10 days the red blood count remained under 3,000,000 in spite of repeated blood transfusions which were given at body temperature with no untoward reactions. The icterus index reached its peak of 44 on January 22 and then decreased gradually.

On January 26 the leukocyte count had risen to 12,600 with 68 per cent granulocytes. Of these 15 per cent were band forms. Toxic granulation was present.

On January 29 the erythrocyte count was 3,060,000 and the icteric index 28. Auto-agglutination could *no longer* be demonstrated.

On February 6 a left subdiaphragmatic abscess was incised and drained. Subsequently the patient made a gradual recovery without any further incident. He received a total of 12 blood transfusions, 21 units of plasma, and 6,140,000 units of penicillin.

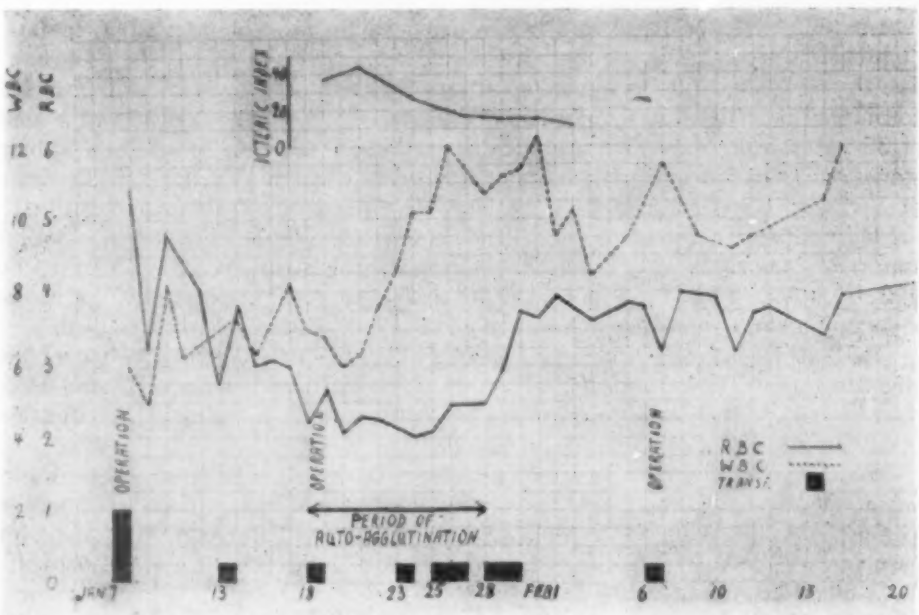


FIG. 1. The levels of the red blood cell and white blood cell counts following discontinuance of sulfonamide therapy on January 9. The period of auto-agglutination is indicated.

During the period of auto-agglutination (figure 1) repeated washing of the patient's cells with normal saline eliminated the agglutination, with other sera. This suggested that the agglutination, of the patient's unwashed cells with all sera, including "anti-B" rabbit antisera, was caused by the adsorption of agglutinins to the cell surface. Serial dilutions of the patient's serum set up with "O" cells at 4° C., as well as slide tests of patient's serum with type "A" and "O" cells, examined microscopically, failed to show definite evidence of "cold" isoagglutinins as described by Dameshek.[2]

## SUMMARY

A case is presented showing hemolytic anemia, transient appearance of "cold" auto-agglutinins, and lack of leukocytic response to bacterial infection following administration of sulfonamides.

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## CALCIFICATION OF THE MYOCARDIUM *

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In 1924 Scholz [1] assembled from the literature 30 cases of calcification of the myocardium. He classified 14 as due to myocarditis. Oheim [2] has reported that minute deposits of calcium in the myocardium are not uncommon in fatal diphtheritic myocarditis. Scholz attributed three cases to coronary occlusion; five to sepsis and four to extension from calcification of the pericardium. He considered four the result of "calcium metastasis": Siebenmann's case of a man of 36 years with "extensive cystic degeneration of the long bones" and kidney stones, was thought by Siebenmann "one of plain calcium metastasis in the sense of Virchow, being secondary to the bone dissolving osteomalacic process." In the light of present day knowledge, this was obviously a case of hyperparathyroidism. A similar case was reported by Dawson and Struthers in 1923 (cited by Hanes [3]). Hanes in 1939 published the first instance of calcium deposits in the myocardium recognized by the author as the result of hyperparathyroidism.

In 1940 Brown and Evans [4] collected 14 cases of massive calcification of the myocardium. They, Redfearn,[5] Parkinson, Bedford and Thomson,[6] and Borman [7] have added four more original cases with autopsies. Massive calcification is usually the result of coronary occlusion.

Scholz made the first roentgenologic diagnosis of massive calcification. Parkinson, Bedford and Thomson have made the diagnosis in two cases (the second patient was still living at the time of their paper), and Borman [7] diagnosed his case in life. Roesler [8] discusses the diagnosis in his textbook and Sosman [9] in 1943 mentions seven cases. The diagnosis may have been made much oftener, but not a great many persons with such extensive infarction live long enough for calcification to be laid down.

The differential diagnosis involves chiefly calcification of the pericardium with perhaps extension into the myocardium, as reported by Clark.[10] It is important to make the distinction: if the calcification is limited to the pericardium and symptoms and signs of constriction are present, operative procedures may effect a cure.

Korinek [11] mentioned calcification of the coronary arteries and of the thoracic aorta in the differential diagnosis. He also added extension of calcification of the annulus fibrosus and presented exquisite plates of such a case. In his discussion, however, he considered that calcification of the myocardium sufficient to be picked up roentgenologically was usually a sequel of cardiac aneurysm. Apparently he had not personally encountered such a case.

* Read before Fulton County Medical Society, February 7, 1946.
From Emory University School of Medicine, Department of Internal Medicine.

From the cardiac service of the General Hospital of Mexico City and the National Institute of Cardiology, Dorbecker [12] has reported seven cases of calcification of the mitral valve, three of the annulus fibrosus, six of the aortic valve and none of infarction.

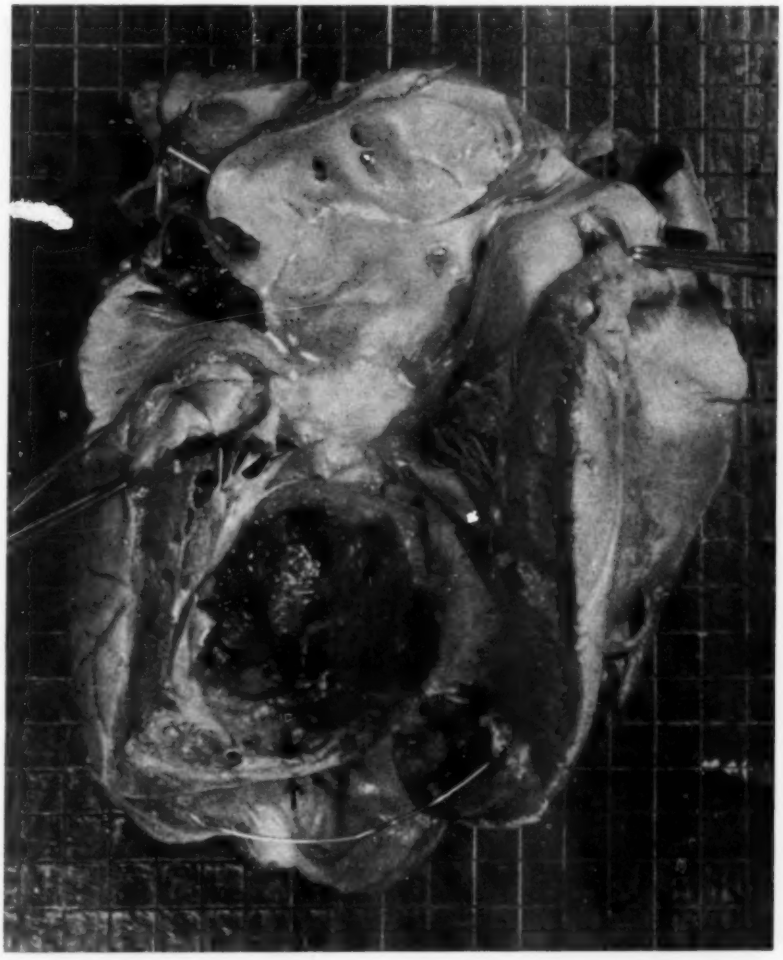

FIG. 1. The left ventricle has been op' ed in the usual manner to expose the ballooning of the aneurysm and the thinness of the wall at the apex. The wire lies over the adherent pericardium. The background is divided into one centimeter squares.

## CASE REPORT

In the spring of 1936, Mr. T., aged 59 years, considered himself in perfect health. Becoming concerned, however, over the sudden death of two friends, he secured additional life insurance. His blood pressure was 140 mm. of Hg systolic and 80 mm. diastolic.

On Saturday, May 2, and again on Sunday, Mr. T. played 27 holes of golf. Monday morning he awakened with a severe pain in the region of the xiphoid. The pain radiated through to the back, and had extended up under the shoulder blades by

the time the nearest doctor got there. This doctor found his blood pressure 174/94; he made a diagnosis of coronary thrombosis. On May 7 the retinal arteries were observed by me to be moderately sclerotic and the heart sounds very muffled. An electrocardiogram revealed an elevation of the S–T segment in Lead I with a depression in Lead III.

FIG. 2. Postmortem roentgenogram of the heart showing the calcification. The pericardium adherent to the apex may also be seen.

In September 1936 Mr. T. returned to work. He was not examined again until October, 1939. His blood pressure then was 164/120 and pulse 128. Fluoroscopic examination showed moderate enlargement of the heart with aneurysm of the left ventricle, and a tortuous, slightly dilated aorta. The electrocardiogram was diagnosed

as indicating an old infarction of the anterior wall with left bundle branch block. A year later his blood pressure was 130/114.

In the spring of 1945 Mr. T. began to experience from time to time pain across the upper sternum usually relieved by aspirin, and his activities were curtailed by undue tiring and breathlessness on exertion. On November 7 pain more severe than usual radiating up the sides of the neck caused him to call me. His blood pressure that morning was 134/100, the pulse 92. An electrocardiogram on November 8 showed no particular change from that in 1939.

November 16, in spite of paroxysmal cough and orthopnea, he came to my office. He weighed 118 pounds. Fluoroscopic examination, done hurriedly because of his breathless condition, showed further enlargement of the heart. Digitalis was prescribed, and frequent injections of salyrgan and aminophylline were started. On November 23, 700 c.c. of clear fluid were withdrawn from the left pleural cavity. Two weeks later Cheyne-Stokes respiration, noted for the first time, was promptly relieved by 0.5 gm. of aminophylline intravenously. The next day he had another severe attack, the periods of apnea lasting 30 seconds. He and his family refused to consider hospitalization. After that there were wide fluctuations in his general appearance: some days his color was good and he breathed comfortably; on others he was cyanotic, with respiratory distress and strutting of the veins of the neck. On January 9, 1946 he turned over unaided and died quietly.

*Autopsy:* The anterior surface of the left ventricle and the apex felt like bone. The pericardium was plastered against this part of the heart and there were also adhesions between the heart and the diaphragmatic surface of the pericardium. The heart was filled with clotted blood; the clots in the right ventricle were apparently post mortem, but those in the auricular appendages and over the infarcted area showed signs of organization. After removal of the clots the heart weighed 520 grams. The right coronary had been occluded recently about 1 cm. from its ostium. The anterior descending branch of the left coronary had been obliterated about 2 cm. below the bifurcation. Distal to this the heart was ballooned out and largely calcified. The infarcted area was roughly circular, 8 cm. in diameter; its inner surface was rough. It involved the apex, the anterior part of the left ventricle and the anterior centimeter of the interventricular septum. This area measured 0.3 to 0.4 cm. in thickness in contrast to an average thickness of 1.5 cm. for the remainder of the left ventricle. The valves were essentially normal. Rather severe grade of sclerosis was noted in the aorta. The right lung was crepitant throughout; there were many infarcts in the left lung with pleural effusion.

## Summary

A man 59 years of age experienced massive myocardial infarction on May 4, 1936. From September 1, 1936 to November 7, 1945 he was able to carry out his duties as vice president of a large concern, with apparently no cardiac symptoms until about nine years after the thrombosis. He died January 9, 1946.

Cardiac aneurysm was recognized fluoroscopically in 1939. It is believed that a more prolonged fluoroscopic examination on November 16, 1945, or an antemortem plate would have revealed the massive calcification of the myocardium.

As Scholz [1] said in 1924, "It may be worth noting that this apparent elimination of so large a portion of the heart muscle causes very little distress to the patient unless the conduction system of the heart happens to be interfered with by the calcifying process."

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## COMPLETE HEART BLOCK IN CALCAREOUS AORTIC STENOSIS *

By H. Warshawsky, M.D., F.A.C.P., and Wm. Abramson, Major, M.C.,
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The earliest recorded case of calcified stenosed aortic valve is that reported by Bonet in 1679 included in a series of case reports with autopsies; this was a postmortem finding in a Parisian tailor who dropped dead in the street.[1]

Calcareous aortic stenosis has been the subject of considerable discussion for many years. As a result, it has become a well-recognized clinical entity which is, however, frequently undiagnosed because of the scarcity or absence of subjective symptoms. Objectively, there is often a dearth of physical signs, so that the condition becomes recognized only at postmortem examination. A fairly recent development is the demonstration of calcific masses in the aortic valve leaflets, annulus, or both, as seen by fluoroscopy.[2]

The etiology of calcareous aortic stenosis is still the subject of debate, although it is quite generally agreed that there is a distinct pathologic entity originally described by Mönckeberg. Christian [4] was convinced of the specificity of this condition. In addition, however, there are those cases in which calcification

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From the Medical Service, U. S. Veterans Hospital, Dayton, Ohio.
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is superimposed upon the residuals of inflammatory valvular changes, such as occurs in rheumatic valvular disease and in healed cases of subacute bacterial endocarditis. It is usually agreed that syphilis is a rare precursor of calcification of a valve, if it ever is. Pure Mönckeberg's sclerosis occurs much less commonly than calcific aortic stenosis secondary to rheumatic fever. In a study of 40 cases by Karsner and Koletski [5] only three were believed to represent true Mönckeberg's sclerosis.

An interesting feature of calcareous aortic stenosis is the presence of complete heart block on rare occasions. The latter abnormality is usually listed as being caused by a variety of conditions. According to White,[3] "fibrosis of the bundle of His from coronary arteriosclerosis is the lesion most commonly found in heart block; infiltration by rheumatic, syphilitic or other infectious process, like bacterial endocarditis and calcareous extension from the region of the mitral or aortic valve which is calcified at its base, is occasionally encountered, while congenital defects of the bundle are rare."

Boas [6] stressed the occurrence of heart block in calcareous aortic stenosis. Cohen, Gray, Nash and Fink [7] in a report of nine cases of this disease cite the case of an 84 year old man whose heart at autopsy revealed fibrosis in the interventricular system probably due to an extension of calcific changes from the aortic valve and ring. They believed that this fibrosis in the interventricular system was responsible for auriculo-ventricular dissociation with complete heart block. Dry and Willius [8] made a study of 176 cases of calcareous aortic stenosis in which electrocardiographic records were available. Of these, 63 were examined at post mortem and in this group, there was one case with complete heart block in which the nodular excrescence of calcium extended from the mitral cusp of the aortic valve in such a manner as to involve the bundle of His. Of 85 cases showing marked calcareous aortic stenosis, two showed complete heart block. Reich [9] in a clinico-pathologic correlation of 22 cases of calcific aortic valve stenosis, reported one case with rheumatic etiology which presented both complete heart block and left bundle branch block.

## Case Report

A 52 year old negro male veteran of World War I whose occupation had been that of a laborer, was admitted to the hospital February 8, 1945, with history of onset of symptoms in May 1944, when he first noticed fatigue and discomfort in the anterior left chest and left arm brought on by exertion. This discomfort would last from 20 to 30 minutes at a time, and was usually relieved by rest. There was no nocturnal dyspnea. A private physician in August 1944 told him that he had high blood pressure; at that time he first noticed transient swelling of the feet and shortness of breath on exertion. About this same time he had suffered a convulsive seizure followed by hours of unconsciousness. The veteran was confined to bed by his physician until he was admitted to this Hospital.

*Past Medical History:* Penile sore at 16 years of age. Was given several injections of arsenicals and bismuth at a clinic near his home in Kentucky in 1944. No history of rheumatic fever or other rheumatic manifestations.

*Examination on Admission:* A chronically ill 50 year old negro male who was ambulatory. The cervical veins were somewhat distended but there was no cyanosis or edema. The lower lung fields posteriorly revealed scattered moist and musical râles. The pulse and cardiac impulse were synchronous, but irregular, their rate

being 50 per minute. A systolic thrill was palpated over the aortic area. The heart was markedly enlarged to the left, the apex being located by palpation and percussion in the sixth left interspace at the anterior axillary line. Systolic and diastolic murmurs were audible at the aortic area. The systolic murmur was rough, of great intensity, and heard loudest over the aortic area, although transmitted all over the precordium. The diastolic sound was blowing in character. A third heart sound was audible at the apical area. Blood pressure 190 mm. Hg. systolic and 110 diastolic. Peripheral vessels were sclerotic and tortuous. The abdomen revealed no hepatomegaly, splenomegaly or ascites.

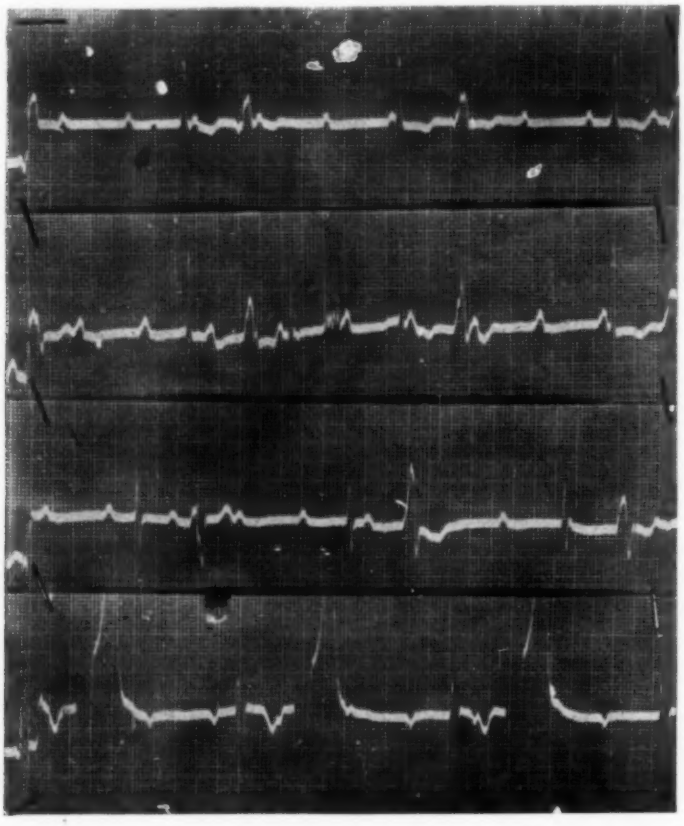

FIG. 1. Electrocardiogram showing complete heart block with auriculoventricular dissociation. Premature ventricular beats follow each normal ventricular complex.

*Laboratory Data:* Urinalysis: specific gravity 1.020; negative albumin and sugar; occasional white blood cells; no red blood cells or casts. Red blood cell count 5,020,000; hemoglobin 16 grams; white blood cells 7,300. Blood Wassermann test negative; Kahn 3; Kline 4. Blood non-protein nitrogen 35.7 and creatinine 1.5 mg. per cent.

Roentgen-ray of the chest revealed a mild degree of congestion in the hilar areas. The cardiac image was markedly enlarged, with a transverse diameter of 18 cm. as contrasted to a chest diameter of 29 cm. The aortic diameter was 6.5 cm.

Electrocardiogram on February 9, 1945, revealed complete heart block with A–V dissociation and many premature ventricular beats (figure 1). There was inversion

of $T_1$; diphasic $T_2$; upright $T_3$ and inverted $T_4$. Left axis deviation was also present. Another electrocardiogram taken on February 10, 1945, was the same except for the absence of premature beats.

The combination of physical findings was somewhat confusing and a diagnosis of aortic stenosis and insufficiency was made. The etiology could not be established with certainty. The absence of a large pulse pressure and Corrigan pulse together with the distinct and pronounced aortic systolic thrill militated against a diagnosis of luetic aortic insufficiency. The most likely etiology was considered to be rheumatism.

FIG. 2. Section of heart showing sclerosed aortic valve and calcific extension to the interventricular septum.

The heart block was attributed clinically to sclerosis involving the bundle of His or a gumma in the same area. The likelihood of impingement upon the membranous ventricular septum with disruption of the bundle of His by a calcific mass extending from a calcified aortic ring was also entertained. The pulse pressure of 80 mm. and the diastolic murmur at the aortic area were considered evidence against the classical calcific aortic stenosis.

*Course in the Hospital:* At no time was there abnormal elevation of temperature. No evidence of heart failure was ever noted on the ward. The patient spent most of his time in and near his bed; he had bathroom privileges. He complained frequently of vertigo and occasionally of substernal distress. On one occasion, he suffered an episode of unconsciousness from which he promptly recovered. This was considered to have been a Stokes-Adams attack. His pulse shortly afterward was 36 and blood pressure 218 mm. Hg systolic and 70 diastolic. During the first few weeks he was given 0.2 gram of bismuth subsalicylate intramuscularly twice weekly and saturated solution of potassium iodide; aminophylline by mouth was given continuously throughout the hospitalization. For a few weeks he had been given $\frac{1}{100}$ grain of atropine sulfate subcutaneously three times daily. On August 3, 1945, he complained of

weakness while reading a paper; his pulse rate was 28 per minute. A few minutes later he died suddenly.

Excerpt from Post Mortem, August 6, 1945: Heart (Gross). The pericardial sac was essentially normal. The heart weighed 780 grams and showed considerable hypertrophy of the left ventricle. Several points of softening were noted in the left myocardium. The subepicardial fat was of normal amount and distribution. The auricles and auricular appendages were normal. The tricuspid valve was normal. The right ventricular chamber was slightly dilated; the musculature was soft. The left ventricle showed considerable hypertrophy of the muscle; the latter measured 2.2 cm. in thickness whereas the interventricular septum measured 2.5 cm.

The posterior leaf of the mitral valve was mainly involved. Here the *chordae tendineae* were thick and shrunken. The free edges were retracted. There was verrucous calcification at the base of the apron, continuous with the aortic involvement. The aortic valve was completely stenotic. The opening was irregularly triangular and elongated, measuring approximately 1.8 cm. at its widest point. There were extensive sclerotic and calcific changes and heaped up verrucous calcification on the ventricular side (figure 2). This verrucous involvement extended directly into the membranous portion of the interventricular septum. In the latter there was a small, nodular, calcific mass measuring approximately 3 mm. in diameter. The myocardium adjacent to this nodular calcification was slightly fibrotic, but otherwise showed no special features. The coronaries exhibited mild atherosclerosis. The ascending aorta showed atheromatous involvement. There was no evidence of luetic aortitis.

Histological examination of sections through the involved valves and myocardium revealed considerable sclerosis with thickening of the valve. At the base of the valve there was increased vascularity with a scattering of a few lymphocytes and monocytes. These showed no particular localization. In the interventricular myocardium adjacent to the nodular calcification considerable replacement fibrosis was present. In one area there was a suggestive Aschoff body. Sections of the remaining myocardium failed to reveal any evidence of similar rheumatic involvement, except for the presence of pseudonodular interstitial connective tissue in the perivascular regions. The conduction system was not visualized. The myocardial fibers exhibited myocardial degeneration consisting of fatty degeneration as well as interstitial fatty infiltration.

The pathology exhibited by this heart is consistent with old rheumatic valvulitis with subsequent fibrosis and calcification.

## Comment

This case of calcareous aortic stenosis is believed to be of rheumatic etiology because of the co-existence of characteristic changes in the mitral valve leaflets. In addition, the presence of aortic insufficiency, too, would seem to be valid ground on which to make this assumption. True Mönckeberg's aortic sclerosis is not associated with clinical evidence of aortic insufficiency. The positive blood serology indicative of syphilis contributed to the confusion. Clinically the presence of the marked systolic thrill in association with a distinct aortic diastolic blow was strong evidence against luetic aortic insufficiency. At autopsy, no evidence of luetic aortitis was found and the coronary ostia were patent. This patient died suddenly, but we believe that his death was related to the complete heart block, rather than the aortic valvular lesion per se. Sudden death is not an uncommon occurrence in true calcareous aortic stenosis. We did not overlook the possibility that the complete heart block in this case could have been due to sclerosis in the septum, secondary to coronary arteriosclerosis. This is a very

common cause of heart block in older people. However, the location of the calcific mass extending from the aortic valve is such as to make it quite certain that this caused impingement on the neuromuscular tissue of the bundle of His.


## Summary

A case of complete heart block is presented which occurred in an individual with rheumatic heart disease characterized clinically by aortic stenosis and insufficiency. The diagnosis of calcific aortic stenosis was entertained because of the characteristic thrill and murmur which usually occur in this condition. It was believed on clinical grounds that calcific extension to the bundle of His was the specific cause of the heart block. The postmortem findings substantiate this conclusion.


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# EDITORIAL

## *RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF GRANULOMA INGUINALE*

GRANULOMA inguinale is a disease of probable venereal origin which holds little interest for the average practitioner, primarily because of the scarcity of such patients in private practice. However, those physicians who work in venereal disease clinics, particularly those below the Mason-Dixon line, find that the diagnosis and therapeutic management of this condition constitute a major problem.

Since the first adequate clinical description of granuloma inguinale by Conyers and Daniels [1] in 1896, many methods of diagnosis and many therapeutic procedures have been given trials with varying degrees of success. Donovan [2] first described the causative organism in 1905, and although he expressed the opinion that it was a protozoan he was unable properly to classify it. Following Donovan's discovery, several investigators claimed that they were able to culture the organism on different types of media, but these claims were not substantiated by reliable workers who tried the same technics. It was not until the work of Anderson, DeMonbreun and Goodpasture [3] that the Donovan body was successfully cultured and classified. These investigators used the yolk of chick embryos as a culture medium, and stated that the organism is a bacillus for which they proposed the name *Donovania granulomatis*. Kornblith [4] made an antigen by grinding a piece of tissue, heavily infected with Donovan bodies, in a mortar with a small amount of saline. After incubating the mixture at 60° C. for two hours on two successive days, and then testing it for sterility, he used it as an antigen by injecting 0.1 c.c. intradermally and observed the reactions in 24 hours. His claim that the antigen is specific is substantiated by the work of Anderson et al.[5] who carried out similar experiments, using a washed suspension of Donovan bodies which had been cultured in the yolk of chick embryos. These observations constitute an important contribution to the diagnosis of this disease. All investigators agree that clinical observation alone does not suffice, but that the presence of the organism must be demonstrated. In most clinics this is done by currettement of the margin of the lesion, staining a thick smear with Wright's or Giemsa stain, and searching for the characteristic intra- and extra-cellular bodies.

[1] CONYERS, J. H., and DANIELS, C. W.: The lupoid form of the so-called groin ulceration of this colony, British Guiana Med. Ann., 1896, viii, 13–29.

[2] DONOVAN, C.: Ulcerating granuloma of the pudenda, Indian Med. Gaz., 1905, xl, 414.

[3] ANDERSON, K., DEMONBREUN, W. A., and GOODPASTURE, E. W.: An etiologic consideration of *Donovania granulomatis* cultivated from granuloma inguinale (three cases) in embryonic yolk, Jr. Exper. Med., 1945, lxxxi, 25.

[4] KORNBLITH, B. A.: The intradermal reaction as an aid in diagnosis of granuloma inguinale, New York State Jr. Med., 1944, xliv, 2476.

[5] ANDERSON, K., GOODPASTURE, E. W., and DEMONBREUN, W. A.: Immunologic relationship of *Donovania granulomatis* to granuloma inguinale, Jr. Exper. Med., 1945, lxxxi, 41.

An interesting sidelight is the fact that, although we can accurately diagnose this disease, we do not as yet know the mode of transmission and thus far the incubation period is still a mystery. Investigation of contacts has been fruitless, as the sexual partners of patients with extensive lesions have been proved to be clinically free of the disease. Two women with extensive involvement of the perineum were personally observed throughout their pregnancies in the Dermatology Clinic at the University Hospital in Baltimore. Both of these patients were delivered of normal living children who subsequently did not show any clinical evidence of granuloma inguinale. One theory of the mode of transmission is via an insect vector such as the *Pediculus pubis*. However, this theory seems untenable in view of the extreme rarity of pediculosis in the Negro, and the fact that the vast majority of these cases occur in colored people.

For many years following the original description it was assumed that granuloma inguinale was a local disease of the skin. It is a very destructive process and in some cases has been known to completely amputate the male genitalia as it progressed. Not until 1939, when Greenblatt and his coworkers [6] demonstrated the presence of Donovan bodies in lymph nodes, did it become apparent that the disease might cause systemic involvement. In 1944, Lyford, Scott, and Johnson [7] reported three cases of polyarticular arthritis and osteomyelitis due to granuloma inguinale. In the same year Pund and McInnes [8] reported six deaths due to the disease and from postmortem findings concluded that the process may spread by way of the lymphatics or by surface continuity. From these reports we are forced to realize that we are dealing with a disease process which not only causes marked local destruction, but in some instances becomes generalized, and results in death.

Conyers and Daniels,[1] in their original report, advised surgical removal of the lesions. The first satisfactory chemotherapeutic measure was reported by Aragao and Vianna [9] in 1913. They advised intravenous administration of tartar emetic (antimony and potassium tartrate) in freshly prepared aqueous solution. Following this report, further investigations were made of the use of this drug by Pardo,[10] Low and Newham,[11] Randall, Small and Belk,[12] Johns and Gage,[13] Weinberg,[14] Hazen, et al.[15] Cole,[16] and

[6] Greenblatt, R. B., Dienst, R. B., Pund, E. R., and Torpin, R.: Experimental and clinical granuloma inguinale, Jr. Am. Med. Assoc., 1939, cxiii, 1109.

[7] Lyford, John, III, Scott, R. B., and Johnson, R. W., Jr.: Polyarticular arthritis and osteomyelitis due to granuloma inguinale, Am. Jr. Syph., Gonor. and Ven. Dis., 1944, xxviii, 588.

[8] Pund, E. R., and McInnes, G. F.: Granuloma inguinale: a cause of death, Clinics, 1944, iii, 221.

[9] Aragao, H. deB., and Vianna, G.: Pesquizas sobre o granuloma venereo, Mem. do Inst. Oswaldo Cruz., 1913, v, 211.

[10] Pardo, V.: Ulcerating granuloma of the pudenda, Jr. Cut. Dis., 1918, iii, 206.

[11] Low, G. C., and Newham, H. B.: A case of ulcerating granuloma successfully treated by intravenous injections of antimony, Brit. Med. Jr., 1916, ii, 387.

[12] Randall, A., Small, J. C., and Belk, W. P.: Tropical inguinal granuloma in the Eastern United States, Jr. Urol., 1921, v, 539.

[13] Johns, F. M., and Gage, I. M.: Granuloma inguinale and cultural studies of Donovan bodies, Internat. Clin., 1924, iv, 15.

Manson-Bahr.[17] All of these workers agreed that tartar emetic has curative value in the treatment of granuloma inguinale. Randall and his co-workers [12] stated that the results from the use of this drug in the treatment of granuloma inguinale were as striking as the results from the use of arsphenamine in syphilis. However, Cole [16] noted frequent relapses and Fraser [18] reported 62.5 per cent failures in his series of cases. In 1933 Williamson [19] investigated the use of another antimony compound, Fuadin, which he claimed to be more rapidly effective than tartar emetic and less reactive. In 1942 Robinson, Robinson, Jr., Mays and Shelley [20] reported a series of 62 cases. There were 39.2 per cent failures in those cases treated with antimony compounds. Excision of localized lesions was found to be an effective treatment in their hands, and this is still an acceptable therapeutic measure. Even after successful chemotherapy surgical intervention for the removal of scar tissue and the relief of lymphatic obstruction may be necessary. There is one general point of agreement in all the reports concerning the use of antimony compounds and that is expressed in the statement of Brandt and Gatewood,[21] "The effect of antimony compounds is pronounced in the early phases of the disease and decreases in direct ratio to its duration."

The advent of each new drug has acted as a stimulus to its trial in the treatment of granuloma inguinale. Ross [22] used sulfapyridine and claimed excellent results but no confirmation has been forthcoming. Nelson [23] and Haserick [24] proved that penicillin had no value in this disease.

The demonstration of the bacillary nature of the Donovan body by Anderson and her associates [3] led Barton, Craig, Schwemlein, and Bauer [25] to try streptomycin as a therapeutic measure. From this early report and others since there are indications that this drug surpasses antimony compounds in healing the lesions and that the percentage of relapses is much smaller.

The first study made by Barton and his associates was begun in February

[14] Weinberg, M.: Granuloma inguinale, Jr. Urol., 1923, ix, 505.

[15] Hazen, H. H., Howard, W. J., Freeman, C. W., and Scull, R. H.: The treatment of granuloma in the negro, Jr. Am. Med. Assoc., 1932, xcix, 1410.

[16] Cole, H. N.: Venereal diseases with particular reference to granuloma inguinale and lymphogranuloma inguinale, Penn. Med. Jr., 1937, xl, 803.

[17] Manson-Bahr, P. H.: Ulcerating granuloma of the pudenda. Manson's Tropical Diseases, 1940, Williams and Wilkins Co., Baltimore.

[18] Fraser, A. R.: Granuloma inguinale, Brit. Jr. Dermat., 1925, xxxvii, 14.

[19] Williamson, T. V., Anderson, J. W., Kimbrough, R., and Dodson, A. L.: Specific effect of "Fouadin" (Fuadin) on granuloma inguinale: preliminary report, Jr. Am. Med. Assoc., 1933, c, 1671.

[20] Robinson, H. M., Robinson, H. M., Jr., Shelley, H. S., and Mays, H. B.: The treatment of granuloma inguinale, South. Med. Jr., 1942, xxxv, 889.

[21] Brandt, R., and Gatewood, T. S.: Early diagnosis of granuloma inguinale, Am. Jr. Syph., Gonor. and Ven. Dis., 1945, lii, 182.

[22] Ross, A. O. F.: Granuloma inguinale treated with M & B 693, Lancet, 1939, i, 26.

[23] Nelson, R. A.: Penicillin in treatment of granuloma inguinale, Am. Jr. Syph., Gonor. and Ven. Dis., 1944, xxviii, 611.

[24] Haserick, J. R.: The failure of penicillin in the treatment of granuloma inguinale, Arch. Dermat. and Syph., 1945, lii, 182.

[25] Barton, R. L., Craig, R. M., Schwemlein, G. X., and Bauer, T. J.: Granuloma inguinale treated with streptomycin, Arch. Dermat. and Syph., 1947, lvi, 1.

1946. They were able to demonstrate healing of the lesions in all of their cases before their limited supply of streptomycin was exhausted. One case was followed for two and a half months and no relapse was observed, but two of their cases developed new lesions because of inadequate dosage and the inability to continue treatment because the supply of drug had been exhausted. One noteworthy fact was established by this trial, however, and that was that the Donovan bodies disappeared from the lesions in from 10 to 20 days. In June 1947, Kupperman, Greenblatt and Dienst [26] reported on the results of their experiments with streptomycin in the treatment of granuloma inguinale. They treated 32 patients in whom they were able to establish the diagnosis of the disease by demonstrating the presence of Donovan bodies in stained smears from the lesions. In some of their cases the organisms disappeared from the lesions as early as the fourth or fifth day of treatment and all patients were free of the specific organisms at the end of 14 days. Their patients had almost immediate relief from pain following the institution of therapy. They noted recurrences in three cases, but none of these had received adequate dosage. There was complete involution of lesions in the remainder of the cases. This report was made at the American Medical Association Convention in June 1947. The discussion was opened by Dr. R. R. Kierland and Dr. Donald Pillsbury both of whom were enthusiastic about the results of this new form of therapy.

The reports to date therefore suggest that streptomycin will prove to be a specific for this debilitating and destructive disease process. If further experience proves this to be the case it is to be hoped that public funds will be forthcoming so that the new treatment may be made available to the indigent cases who comprise the majority of those afflicted with this disease.

H. M. Robinson, Jr.

[26] Kupperman, H. S., Greenblatt, R. B., and Dienst, R. B.: Streptomycin in the therapy of granuloma inguinale. Presented at the Convention of the Am. Med. Assoc., June 12, 1947.

# REVIEWS

*Early Ambulation and Related Procedures in Surgical Management.* By DANIEL J. LEITHAUSER, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit, Michigan. 232 pages; 23 × 15 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1946. Price, $4.50.

This is an excellent survey of the factors involved in early ambulation. Physiological principles of early ambulation are reviewed in a comprehensive and concise manner with clear differentiation of the terms "early ambulation" as opposed to "early rising."

The literature bearing on the subject is summarized and an excellent author reference listing is given.

Space is devoted to discussion of the physiopathological effects on the systems of the body of surgical procedures, and the accentuation of these effects by inactivity. The employment of various surgical technics and incisions is discussed in relationship to early ambulation. The importance of following physiologic principles in pre- and post-operative care, as well as at operation, is stressed.

The results in a remarkable series of 2047 cases are reviewed. In this series, there was no evidence of pulmonary embolism and only two cases of thrombophlebitis, the latter occurring early in the series. Wound disruption, which the author believes occurs on the fifth to ninth day postoperatively, is discussed in its relationship to early ambulation.

Detailed information is included regarding postoperative management, with an excellent description, well illustrated, of the technic of early ambulation.

This book is a valuable contribution to an important subject that requires constant emphasis. It could be improved by greater conciseness and elimination of extraneous material. Personal testimonials in a book of this character do not add to its intrinsic value.

G. H. Y.

*Pulmonary Tuberculosis:* A Handbook for Students and Practitioners. By R. Y. KEERS, M.D., M.R.C.P. (Edin.), F.R.F.P.S. (Glas.), Medical Director, Red Cross Sanatoria of Scotland, etc., and B. G. RIGDEN, M.R.C.S. (Eng.), L.R.C.P. (Lond.), First Assistant Medical Officer, Red Cross Sanatoria of Scotland, etc., with a Foreword by F. H. YOUNG, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H., Physician, Brompton Hospital for Consumption and Diseases of the Chest, etc. 227 pages; 19 × 12.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, $5.00.

In this compact volume, the authors cover the entire disease in a simple, yet complete manner, so that it provides the answer to most questions relative to the disease. In general, the authors are in agreement with most of the present trends as accepted in this country.

Of particular note is the chapter "Examination of the Patient," in which the authors have deviated from the old pattern of emphasizing the physical examination. They have correctly given the roentgen examination a position second only to the history of the case, and have placed the physical examination as the least important of the diagnostic procedures.

The roentgenograms reproduced in the book are excellent, both from the standpoint of sharp delineation, and in the presentation of the various types of the disease and collapse therapy. These should prove to be of special interest to the reader.

The section devoted to collapse therapy is complete, and an evaluation of the various procedures is presented in a critical, but not confusing manner. A rather clear picture of the indications and contraindications of each method is offered.

The chapter dealing with "complications" is very good. Exception might be taken, however, to the author's rather radical policy as to therapeutic abortion in pregnant tuberculous women. In the major clinics in this country the indications for abortion under these circumstances are more restricted.

L. M. S.

*Microbial Antagonisms and Antibiotic Substances.* Revised Edition. By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers University; Microbiologist, New Jersey Agricultural Experiment Station. 415 pages; 16 × 24.5 cm. The Commonwealth Fund, 41 E. 57th St., New York, N. Y. 1947. Price, $4.00.

Because of the rapid progress in knowledge of the formation, isolation and application of antibiotics, Dr. Waksman has revised the first edition of his well known work. Streptomycin and penicillin are adequately discussed, bringing the reader up to date with the findings of current research.

Dr. Waksman includes an exhaustive review of the literature dealing with the habitats, interrelationships and antagonisms among microörganisms. Bacteria, fungi, and animal forms acting as antagonists are discussed. Of significant practical value are the sections on the chemical nature of these substances and the various methods of measuring antibiotic action. Well written, sufficiently illustrated, this book serves as a basic text and is of inestimable value to the physician desiring information relative to the use of antibiotics as chemotherapeutic agents in the control of infection.

T. E. W.

*War Stress and Neurotic Illness.* Second Edition. By ABRAM KARDINER, M.D., with the collaboration of HERBERT SPIEGEL, M.D. 428 pages; 21.5 × 14.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1947. Price, $4.50.

This book is written only for the psychiatric specialist, and more specifically for those working mainly with veteran or civilian traumatic neuroses.

The authors start by presenting an excellent discussion of the clinical pictures seen in both acute and chronic traumatic neuroses, and point out the true, but not too well accepted fact that a compensation factor hinders recovery. The main portion of the book is devoted to a theoretical evaluation and discussion of the data in an attempt to determine the nature of the traumatic neurosis. The authors approach this with a combination of reflexology and desexualized psychoanalysis: They arrive at the conclusion that traumatic neurosis is basically different from other psychiatric illness. There are no conclusions reached as to why some persons develop illness and others do not under similar circumstances, and no significant changes in therapy are recommended.

H. W. N.

## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Beiträge zur Kenntnis der Blutgerinnung.* By W. K. RIEBEN. 96 pages; 22.5 × 15.5 cm. (paper bound). 1947. Benno Schwabe & Company, Basel; imported by Grune & Stratton, Inc., New York. Price, 9 fr.

*The Clinical Examination of the Nervous System* (8th Edition). By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, etc. 380 pages; 19 × 13 cm. 1947. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $4.50.

*Cornell Conferences on Therapy* (Volume II). Edited by HARRY GOLD, M.D., Managing Editor, et al. 354 pages; 21 × 14 cm. 1947. The Macmillan Company, New York. Price, $3.75.

*Dania Polyglotta.* Under the direction of K. SCHMIDT-PHISELDECK, with the collaboration of HENNING EINERSEN. 299 pages; 24.5 × 16.5 cm. (paper bound). 1947. Bibliotheque Royale, Copenhagen. Price, 1 crown; Vol. 1901–1944, 3 crowns.

*Endocrinology (Experimental and Clinical): Being Section III of Excerpta Medica.* (A Complete Monthly Abstracting Service of the World Medical Literature Comprising 15 Sections and Covering the Whole Field of Theoretical and Clinical Medicine.) Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology, University of Amsterdam, etc. 64 pages; 25 × 16.5 cm. (paper). 1947. The Williams & Wilkins Company, Baltimore. Price, Subscription: $15.00.

*Endogenous Endocrinotherapy,* including The Causal Cure of Cancer: Compendium, by DR. JULES SAMUELS, Specialist for endogenous endocrinotherapy, Amsterdam. 539 pages; 25 × 17.5 cm. 1947. Holdert & Company, Ltd., Amsterdam. Price, f. 24.

*Headache.* By LOUIS G. MOENCH, M.D., Assistant Clinical Professor of Medicine, University of Utah School of Medicine, etc. 207 pages; 21.5 × 14.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, $3.50.

*Hodgkin's Disease and Allied Disorders.* By HENRY JACKSON, JR., A.B., M.D., Assistant Professor of Medicine, Harvard Medical School, etc., and FREDERIC PARKER, JR., A.B., M.D., Associate Professor of Pathology, Harvard Medical School, etc. 177 pages; 28.5 × 19.5 cm. 1947. Oxford University Press, New York. Price, $6.50.

*A Neuro-Vascular Syndrome Related to Vitamin Deficiency.* By HENDRIK SMITSKAMP. 114 pages; 24.5 × 15.5 cm. (paper bound). 1947. Scheltema & Holkema's Boekhandel en Uitgeversmaatschappij N.V., Amsterdam. Privately printed, no copies available.

*Physical Medicine in General Practice* (Second Edition, Revised and Enlarged). By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hospital, etc. With a chapter on Medical Rehabilitation by DR. SIDNEY LICHT. 686

pages; 24.5 × 16.5 cm. 1947. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $8.00.

*Physiology of Man in the Desert.* By E. F. ADOLPH and Associates, Department of Physiology, University of Rochester. 357 pages; 23.5 × 16 cm. 1947. Interscience Publishers, Inc., New York. Price, $6.50.

*The Scientists Speak.* Edited by WARREN WEAVER. 369 pages; 22 × 14.5 cm. 1947. Boni & Gaer, Inc., New York. Price, $3.75.

*The Selected Writings of Benjamin Rush.* Edited by DAGOBERT D. RUNES. 433 pages; 21 × 14 cm. 1947. The Philosophical Library, Inc., New York. Price, $5.00.

*Spezifische Typhustherapie mit einem Beitrag zur Typhuspathogenese.* By DOZENT DR. FERDINAND NAGL and DR. OSKAR LACHNER. 63 pages; 24 × 17 cm. (paper bound). 1947. Distributed in U. S. A. by Grune & Stratton, Inc., New York. Price, $2.20.

# COLLEGE NEWS NOTES

### American Board of Internal Medicine Announces Forthcoming Oral Examinations

Oral examinations in the American Board of Internal Medicine will be conducted at San Francisco in April, 1948, and in Chicago in June, 1948, both periods immediately preceding the Annual Sessions of the American College of Physicians and the American Medical Association, respectively.

The closing date for registration for oral examinations is February 1, 1948.

The Board also announced the next written examination for October 18, 1948, with closing date for registration, June 1, 1948.

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### Meeting Dates

The 76th Annual Meeting of The American Public Health Association will take place at Boston, Mass., the week of November 8, 1948.

The Centenary Year Annual Session of The Medical Society of the State of Pennsylvania will occur October 4–7, 1948, at Philadelphia, Pa.

The 1948 annual meeting of the State Medical Society of Wisconsin will be held at Milwaukee, Wis., October 4–6, 1948.

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### Life Insurance Medical Research Fund Fellowships

The Life Insurance Medical Research Fund, 2 E. 103rd St., New York 29, N. Y., has announced that it will award about twelve fellowships for the year beginning July, 1948, to support laboratory and clinical investigation of cardiovascular problems. The annual stipend is stated to be between $2,500.00 and $3,500.00. Candidates must have an M.D. or Ph.D. or equivalent degree. The closing date for receipt of applications is January 15, 1948.

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The Faculty of the Medical School of the University of California announces the following postgraduate courses of interest to internists: Hematology and Blood Disorders, February 16 through 20, 1948; Internal Medicine and General Surgery, June 21 through 25, 1948.

Requests for detailed information should be addressed to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

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### 1948 Nominations, American College of Physicians

At the 1948 Annual Business Meeting of the College at San Francisco, April 22, elections will be held for (a) Elective Offices, including President-Elect, First, Second and Third Vice Presidents; (b) Five members of the Board of Regents to fill vacancies of those whose terms expire in 1948; (c) Twenty members of the Board of Governors to fill vacancies of those whose terms expire in 1948.

Tenure of office of Regents is limited to two consecutive terms; of Governors,

to three consecutive terms. Thus some present incumbents are eligible for re-election, while others are not. The list of present incumbents is published elsewhere in this issue.

The By-Laws provide that the nominees for the Elective Offices of President-Elect, First, Second and Third Vice Presidents shall be published to the members of the College thirty days in advance of the Annual Business Meeting, but that nominees for the Board of Regents and Board of Governors may be announced directly at the Annual Business Meeting. It is, therefore, necessary that the nominees for the Elective Offices be selected in early January or February, 1948, but nominees for the Board of Regents and Board of Governors may be selected at greater leisure, but adequately in time for submission at the Business Meeting.

The Committee on Nominations, through its Chairman, Dr. William D. Stroud, 1011 Clinton St., Philadelphia 7, Pa., will gladly receive suggestions from FELLOWS and MASTERS concerning nominees for any of the posts to be filled, providing such suggestions are forwarded promptly after publication of this notice.

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### CORRECTION—COMMITTEE CHAIRMEN SAN FRANCISCO ANNUAL SESSION

Correction is herein recorded of an error in the announcement of Committee Chairmen for the San Francisco Annual Session of The American College of Physicians, April 19–23, 1948, as published in the September, 1947, issue of this journal.

Hugh J. Morgan, M.D., President (Program of Morning Lectures and Afternoon General Sessions)
Vanderbilt University Hospital
Nashville, Tenn.

William J. Kerr, M.D.
University of California Hospital
San Francisco 22, Calif.

Ernest H. Falconer, M.D.
384 Post Street
San Francisco 8, Calif.

} Co-General Chairmen (Local Arrangements and Programs of Clinics and Panel Discussions)

Dwight L. Wilbur, M.D., Chairman, Committee on Clinics
Sidney J. Shipman, M.D., Chairman, Committee on Entertainment
George S. Johnson, M.D., Chairman, Committee on Hotels and Transportation

Roberto F. Escamilla, M.D., Chairman, Committee on Panel Discussions
William C. Voorsanger, M.D., Chairman, Committee on Publicity
Mrs. Stacy R. Mettier, Chairman, Committee on Ladies' Entertainment

Edward R. Loveland, Executive Secretary—General Manager of the Session and Director of the Technical Exhibit
4200 Pine Street
Philadelphia 4, Pa.

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### A.C.P. COMMITTEE ON POSTGRADUATE COURSES INVITES SUGGESTIONS

The Advisory Committee on Postgraduate Courses of the American College of Physicians invites the members of the College to send into the Executive Offices of the College suggestions about postgraduate courses that are particularly desired. Not only would the Committee like to know the courses in which members are interested, but would gladly receive suggestions about the institutions at which such courses are desired and the directors under whom the courses might be organized.

It is desirable that the Committee be able to determine the number of members

who would support some particular course, because the College cannot afford to organize courses in which there would be inadequate registration.

A number of outstanding men at the Trudeau Sanatorium at Trudeau, N. Y., are willing to organize a course in pulmonary diseases. This undoubtedly would be one of the outstanding courses in this field in the country, and one that a reasonable number of members of the College would subscribe to. However, the Committee will appreciate it if members who would be interested in this course will so inform the Executive Offices of the College before such a course is scheduled. If there are an adequate number, the College will proceed in adding this course to its schedule.

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## Reports on Recent Regional Meetings

### *Virginia A.C.P. Members Hold Interim Meeting*

About 50 members of the American College of Physicians from the State of Virginia held a dinner meeting at the Hotel Roanoke on October 14, in conjunction with the Annual Meeting of the Medical Society of Virginia. Dr. Charles M. Caravati, F.A.C.P., Richmond, was Chairman. Dr. Staige D. Blackford, F.A.C.P., Charlottesville, was elected Chairman for the coming year, and Dr. James Franklin Waddill, F.A.C.P., Norfolk, was re-elected Secretary. Dr. W. Halsey Barker, F.A.C.P., Baltimore, addressed the meeting and there were informal talks by Dr. Walter B. Martin, F.A.C.P., Regent of the College, Norfolk, and by Dr. J. Morrison Hutcheson, F.A.C.P., Richmond.

### *Western Michigan*

A Regional Meeting for Western Michigan was held at the Muskegon Country Club, Muskegon, Mich., on October 29, 1947, under the Secretaryship of Dr. William M. LeFevre, F.A.C.P., Muskegon. The program consisted of the following papers: "Rocky Mountain Spotted Fever" by Dr. Gerald N. Rein, Benton Harbor; "Post-Menopausal Osteoporosis" by Dr. Silas C. Wiersma, Muskegon; "Silicosis in Industry" by Dr. Leland E. Holly, Muskegon. A reception and dinner were held in the evening, and Dr. Howard B. Carroll of Northwestern University delivered an address on "Duodenal Diverticula." The group voted to hold its next meeting at Battle Creek during the Spring of 1948.

### *North Carolina*

On Friday, November 14, 1947, the Regional Meeting for North Carolina was held at Chapel Hill under the Governorship of Paul F. Whitaker, M.D., F.A.C.P., Kinston. Arrangements for the meeting were made by Robert L. McMillan, M.D., F.A.C.P., Winston-Salem, Chairman of the Program Committee, and Edward McG. Hedgpeth was Chairman of Local Arrangements. An afternoon session was held at the University of North Carolina School of Medicine, and the following papers were presented: "The Shoulder-Hand Syndrome," Elbert L. Persons, M.D., F.A.C.P., Durham; "Tropical and Parasitic Infestations in Veterans and Civilians in North Carolina," Thomas T. Mackie, M.D., F.A.C.P., Winston-Salem; "Clinico-Pathological Conference," Kenneth M. Brinkhous, M.D. (by invitation), Chapel Hill, and David Cayer, M.D. (Associate), Winston-Salem; "Effect of Lanatoside C on the Circulation of Patients with Congestive Failure: A Study Using the Technic of Right Heart Catheterization," Eugene A. Stead, Jr., M.D., F.A.C.P., Durham; and "Recent Advancement in the Treatment of Pulmonary Tuberculosis," H. Stuart Willis, M.D. (by invitation), Sanatorium. The evening session took place at the Carolina Inn and consisted of refreshments and an informal dinner with Dr. Whitaker acting as Toastmaster, and Dr. Mackie introducing the guest speaker, President Morgan.

*Tenth Annual Round-up of Eastern Pennsylvanians*

Dr. Edward L. Bortz, Governor for Eastern Pennsylvania and General Chairman of the Program, extended an invitation to members of the College and their guests in Pennsylvania, Southern New Jersey, and Delaware to attend this meeting held at the Warwick Hotel, Philadelphia, Friday, November 21, 1947. Burgess L. Gordon, M.D., F.A.C.P., and Henry F. Page, M.D., F.A.C.P., both of Philadelphia, presided over the afternoon session at which the following papers were presented by Philadelphia physicians. "Psychoanalysis," Kenneth E. Appel, M.D., Ph.D., Sc.D., F.A.C.P.; "Additional Homeostatic Mechanisms," Joseph T. Freeman, M.D. (Associate); "Atypical Pneumonia Simulating Tuberculosis," Daniel B. Pierson, Jr., M.D., F.A.C.P.; "Etiology and Treatment of Leukemia," Lowell A. Erf, M.D., F.A.C.P.; "The Rational Use of Physical Medicine in Geriatrics," Morris A. Bowie, M.D. (by invitation); "Significant Trends in Public Health," Pascal F. Lucchesi, M.D., M.P.H., F.A.C.P. Reception, cocktails, and informal banquet followed the scientific program. Dr. George Morris Piersol, M.A.C.P., was Toastmaster, and there were many distinguished guests, including President Hugh J. Morgan, Treasurer William D. Stroud, Executive Secretary Edward R. Loveland, the Deans and Presidents of Philadelphia medical institutions, and Governors of nearby territories.

*Southeastern Regional Meeting*

Alabama, Florida, Georgia, South Carolina, and Cuba joined, under the General Chairmanship of William C. Blake, M.D., F.A.C.P., Tampa, Fla., to present a two-day program at Tampa, December 8–9, 1947, with Dr. Blake, Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, and Dr. Robert Wilson, Jr., F.A.C.P., Governor for South Carolina, acting as Presiding Officers at the various sessions. The scientific program (Floridan Hotel, Monday morning and afternoon and Tuesday morning) consisted of the following: "Anticoagulant Therapy of Thromboembolic Disease," David F. James, M.D. (by invitation), Atlanta, Ga.; "Anticoagulant Therapy in Coronary Artery Disease," E. Sterling Nichol, M.D., F.A.C.P., Miami, Fla.; "Heart Rate and Circulatory Efficiency," Ashton Graybiel, M.D. (by invitation), Pensacola, Fla.; "The Treatment of Chronic Suppurative Disease of the Lung," Charles J. Donald, Jr., M.D. (by invitation), Birmingham, Ala.; "The Age Factor in Diabetes," George R. Wilkinson, M.D., F.A.C.P., Greenville, S. C.; discussion of the preceding papers opened by Glenville Giddings, M.D., F.A.C.P., Governor for Georgia, Atlanta, Ga.; "Epilepsy: Diagnosis and Treatment," Otto G. Wiedman, M.D., F.A.C.P., Hartford, Conn.; "Curable Forms of Heart Disease," A. Carlton Ernstene, M.D., F.A.C.P., Cleveland, Ohio; "Exophthalmos in Hyperthyroidism," Henry M. Thomas, Jr., M.D., F.A.C.P., Baltimore, Md.; "Clinical Considerations of the Problem of Extrarenal Excretion," Howard M. Odel, M.D., F.A.C.P., Rochester, Minn.; "Transfusion Reactions: A Neglected Medical Problem," John W. Williams, M.D., F.A.C.P., Bay Pines, Fla.; "Surgical Treatment of Hypertension," F. W. Cooper, M.D. (by invitation), Atlanta, Ga.; "The Purpuric State," Robert Wilson, Jr., M.D., F.A.C.P., Charleston, S. C.; "Diagnosis of Congenital Cardiac Anomalies," Harry T. Harper, Jr., M.D., F.A.C.P., Augusta, Ga.; discussion of preceding eight papers opened by Hugh J. Morgan, M.D., F.A.C.P.; "The Clinical Use of Rutin," Karl B. Hanson, MD., F.A.C.P., Jacksonville, Fla.; "Hyperventilation Syndrome," H. Phillip Hampton, M.D. (Associate), Tampa, Fla.; "Experimental Studies on Leukemia," William H. Riser, Jr., M.D. (by invitation), Birmingham, Ala.; "The Low Sodium Diet," Emil M. Isberg, M.D. (Associate), Miami Beach, Fla.; discussion of the preceding four papers opened by Turner Z. Cason, M.D., F.A.C.P. At the dinner Monday evening, Dr. Turner Z. Cason, F.A.C.P., Jacksonville, Governor for Florida, was Toastmaster, and the Guest Speakers were President Hugh J. Morgan, Nashville, Tenn., and Dr. James E. Paullin, Regent and Past President, Atlanta, Ga.

### Dr. Burch Appointed to Head Department of Medicine at Tulane

George E. Burch, M.D., F.A.C P., New Orleans, has been appointed to succeed the late John Herr Musser, M.D., M.A.C.P., as Professor of Medicine and Chairman of the Department of Medicine in the Tulane University of Louisiana School of Medicine. Dr. Burch received his M.D. Degree in 1933 from that institution, and in 1934 joined the staff of its Department of Medicine, in which he has most recently held appointment as Associate Professor of Clinical and Experimental Medicine. From 1939 to 1941 Dr. Burch was Assistant in the Rockefeller Institute for Medical Research, New York, N. Y., serving under Dr. A. E. Cohn. During the war he was appointed Consultant in Medicine (Cardiovascular) to the Surgeon General of the Army.

Dr. Burch is also Senior Visiting Physician to the Charity Hospital of Louisiana, and Visiting Physician to the Touro Infirmary, New Orleans.

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The Royal Australasian College of Physicians, with headquarters in Sydney, Australia, has conferred Honorary Fellowship on Dr. Hugh J. Morgan, President of the American College of Physicians, according to official notice received October 24, 1947, from Dr. S. A. Smith, President of the Royal College.

Dr. Morgan becomes the second Fellow of the American College of Physicians to be so honored, the first having been Dr. Noble Wiley Jones of Victoria, B. C. (formerly of Portland, Ore.), who was the official representative of The American College of Physicians at the inaugural ceremonies of The Royal Australasian College on December 14, 1938.

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Colonel Floyd V. Kilgore, (MC), USA, (Associate), Washington, D. C., has been awarded the Oak Leaf Cluster to the Legion of Merit for his distinguished service in initiating the Army's program for paraplegic cases in the Cushing General Hospital, December, 1944, to October, 1946.

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Colonel Arden Freer, (MC), U. S. Army, Retired, has been appointed Deputy Medical Director of the Veterans Administration.

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The Veterans Administration has announced the development of a center for research in cardiovascular disease at the Mount Alto Hospital, Washington, D. C. George P. Robb, M.D., F.A.C.P., Assistant Medical Director of the Metropolitan Life Insurance Company, New York, N. Y., has supervised the organization of this center and will continue to serve it as Consultant. In addition to research facilities, the center will provide consultative services and opportunities for graduate study and training.

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The National Gastroenterological Association, Inc., has rendered tribute to Hyman I. Goldstein, M.D. (Associate), Camden, N. J., by dedicating the Fifteenth Anniversary Number of its publication, The Review of Gastroenterology, to him on the occasion of his sixtieth birthday.

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The first annual meeting of the California Society of Internal Medicine, which has a membership of more than 400 internists, was held recently in Los Angeles. Members of the College who have been elected officers of the Society are Donald E. Griggs, M.D., F.A.C.P., Los Angeles, President; Harold C. Torbert, M.D., F.A.C.P.,

San Diego; C. Kelly Canelo, M.D., F.A.C.P., San Jose; Frank B. Reardan, M.D. (Associate), Sacramento; and Gurth Carpenter, M.D. (Associate), Beverly Hills; Councilors.

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Finland has an excellent Technical Institute, Teknillinen Korkeakoulu. During the war its library was bombed and totally destroyed.

Martti Levon, Director of the Institute, states that in the remarkable efforts for recovery that the Finns are making, the lack of technical library facilities is a very serious handicap.

It would be a practical act of friendship to a nation that holds America in high regard if Americans should contribute good technical books and periodicals to this library. Any such gifts should be marked for the Institute of Technology, Helsinki, and sent to the Legation of Finland, 2144 Wyoming Ave., N.W., Washington, D. C. Dr. K. T. Jutila, the Finnish Minister, will arrange for their being shipped to Finland.

JOHN HERR MUSSER, B.S., M.D., M.A.C.P.

## *OBITUARIES*

### JOHN HERR MUSSER, B.S., M.D., M.A.C.P.

**Memoir**

When Dr. John Herr Musser, a Master of this College, died on September 5, 1947, at his home in New Orleans, American medicine lost a great internist, the American College of Physicians an ardent supporter, and a long succession of able doctors came to an end.

John Musser, born in Philadelphia on June 9, 1883, came of sturdy Lancaster County stock and was the sixth member of his family in direct descent to become a physician. With such a background and with a father who was one of the outstanding internists of his day and Professor of Clinical Medicine at the University of Pennsylvania for many years, it was not surprising that even during his school days the younger Musser was bent upon following the family tradition. His later achievements as a physician and teacher amply justified the wisdom of his choice of medicine as a career.

Dr. Musser, after attending the famous old William Penn Charter School in Philadelphia, received his Bachelor of Science degree from the University of Pennsylvania in 1905, and his Doctor of Medicine degree from the same institution in 1908. After two years of internship and a course of graduate study at the University of Amsterdam, Dr. Musser entered upon the practice of Internal Medicine in Philadelphia with his father, an association which terminated with the death of Dr. Musser senior in 1912. Young Musser's skill as a physician and ability as a teacher were soon apparent. In 1912 he became visiting physician to the Presbyterian Hospital of Philadelphia, and in 1914 was given a similar title on the staff of the Philadelphia General Hospital. His teaching career began with his appointment in 1914 as Associate in Medicine on the faculty of the School of Medicine of the University of Pennsylvania. A few years later he was made an Assistant Professor of Medicine and in 1920 was promoted to Associate Professor of Medicine in the same medical school.

With the entry of the United States into World War I, Dr. Musser was among the first physicians to renounce a successful practice and give up active teaching to enter the Medical Corps of the United States Army with the rank of first Lieutenant. As a medical officer he proved as popular and as successful as he was as a civilian physician. In 1918 he was sent to France as a member of the University of Pennsylvania's Base Hospital No. 20. While with that organization he earned his majority and became Chief of the Medical Service. Upon his discharge from the Army in 1919, unlike most of his colleagues, he never lost interest in the Medical Department of the Army. He reëntered the Medical Reserve Corps, attaining the rank of Colonel in that organization in 1938. During World War II, he was appointed by the Secretary of War a member of a committee to study the reorganization of the Surgeon General's Office.

Upon the completion of his active duty with the Army in 1919, Dr. Musser returned to Philadelphia to take up his consulting and hospital practice in Internal Medicine and assume more exacting teaching obligations. At this time he took over the added duties of physician to the Howard Hospital of Philadelphia. It required but a few years to convince Dr. Musser that the ever increasing demands and responsibilities of a growing practice left too little time for the pursuit of the more academic and literary medical activities wherein had always lain his greatest interest. A welcome

solution of his problem came when, in 1924, he was appointed Professor of Medicine and Head of the Department of Medicine at Tulane University School of Medicine in New Orleans, a position which he filled with distinction until his death.

The past twenty odd years that Dr. Musser spent in New Orleans represent the most scientifically profitable and productive period of his life. As the first full-time Professor of a clinical department in the medical school at Tulane, he was able to devote successfully his time and energies to teaching, writing and investigation from which he derived much satisfaction and happiness.

Dr. Musser's activities and interests were many and varied. He was known not only as a clinician and medical teacher of unusual distinction but also for his work in the field of Public Health. He served as Director of the Louisiana State Board of Health from 1940 to 1942, during which time he completely reorganized the public health administration machinery of the State for which he was acclaimed by Governor Jones of Louisiana. He served as President of the New Orleans Tuberculosis Association for fourteen years as well as being a Director of the Child Guidance Center and President of the New Orleans Institution for Mental Hygiene.

Regardless of his other interests Dr. Musser was always engaged in literary activity. From 1922 to 1925, he was Editor of the American Journal of the Medical Sciences, having been Assistant Editor for a number of years previously. At the time of his death he was Editor of the New Orleans Medical and Surgical Journal, a responsibility which he assumed in 1927, as well as being a member of the Editorial Board of the Archives of Internal Medicine. He edited and contributed to the important text book "Internal Medicine," which is widely known by his name. The fourth edition appeared in 1945 and the fifth was already in preparation at the time of his death. He revised and edited through four editions the well known textbook on physical diagnosis written by his father, in addition to rewriting two other medical texts. During his life his contributions to contemporary medical journals and presentations before medical societies amounted to well over 100.

Even to the last days of his life his interest in organized medicine never waned, as was evident from his many activities in connection with county and state societies and the American Medical Association. He held many positions in the latter organization. From 1934 on, he was a member of the Council on Medical Education and Hospitals of the American Medical Association. In 1933 to 1934, he was Vice-President and later Chairman of the Section on Pharmacology and Therapeutics of the American Medical Association. From 1937 to 1938, he served as Chairman of the Section on the Practice of Medicine and in 1928 he was a member of the House of Delegates of the American Medical Association.

Dr. Musser was a member of many scientific societies of national importance, notably the Association of American Physicians, American Society of Clinical Investigation, Association for Research in Nervous and Mental Diseases, American Clinical and Climatological Association, College of Physicians of Philadelphia, the Society of Internal Medicine of the Asociación Médica Argentina, Buenos Aires, of which he was a foreign corresponding member, and the American College of Physicians. It was to the last organization that he gave his greatest allegiance and for which he entertained a deep affection. Elected a Fellow in 1920, Dr. Musser served on the Board of Regents from 1926 to 1936, and was President of the College from 1929 to 1930. In these capacities he played a leading rôle in the reorganization of the College, its expansion and development. Throughout his long association with the College he proved himself an indefatigable worker on many committees, including some years of service on the Credentials Committee. In recognition of his years of unselfish devotion, the College bestowed upon him, in 1947, its greatest honor, a Mastership. No group feels more keenly the loss of Dr. Musser than do his loyal friends of the American College of Physicians, especially those who, privileged to work

closely with him on many occasions, came to depend upon his wisdom and good judgment.

Of the many honors that were bestowed on Dr. Musser there were none that brought him greater satisfaction than his election a few years ago as an Alumni Representative to the Board of Trustees of his alma mater and the Alumni Award of Merit of the University of Pennsylvania School of Medicine which he received in 1940. Dr. Musser was not only a diplomate of the American Board of Internal Medicine, but for a number of years served as a member of that certifying body.

It was not so much Dr. Musser's lasting contributions to American medicine and to medical education in this country that so endeared him to all with whom he came in contact as his remarkable personality and charm. His irresistible sense of humor and unfailing cheerfulness were tempered with poise and equanimity. The patience, tolerance and unselfishness characteristic of a great gentleman marked his every act. Yet, with all, he possessed dogged determination and a fearlessness of spirit that enabled him to meet all serious issues with uncompromising honesty. The last years of his full and useful life were marred by serious illness, the disastrous results of which he fully appreciated. In spite of irksome disability and discomfort he never lost interest in his work and to the very last day of his life faced each problem with uncomplaining courage.

His widow, the former Marguerite Hopkinson, his daughter, Mrs. Thomas L. Avengo, four grandchildren, and his sister, Mrs. Richard M. Pearce, are the only surviving members of his immediate family. To them this College extends sincere and heartfelt sympathy. Their loss, irreparable as it is, is not theirs alone; it is shared by all whose good fortune it has been to count as a friend John Musser, teacher, author, investigator, and above all a great understanding physician.

GEORGE MORRIS PIERSOL, M.D., M.A.C.P.,
Secretary-General, ACP

## DR. LAURENCE COLEMAN MILSTEAD

Laurence Coleman Milstead, M.D., F.A.C.P., formerly of Allentown, Pa., died August 31, 1947.

Dr. Milstead was born in Washington, D. C., on September 5, 1899. His collegiate and medical studies were carried out in Georgetown University from which he obtained the degree of Doctor of Medicine in 1924. He served as intern in the Georgetown University Hospital, and then held positions for over three years as assistant clinical pathologist in various Washington hospitals. He was appointed clinical pathologist in the Sacred Heart Hospital, Allentown, Pa., and held this position until 1940. During this time he obtained the respect of local physicians for the thorough knowledge and method of his many presentations of clinical material.

In 1940 Dr. Milstead opened a private laboratory and engaged in consultative work, but left this behind to enter the Army as a Major in 1942. His military record, which continued until June of 1947, included service with the 220th General Hospital in France. Resuming civilian life, Dr. Milstead became pathologist to the St. Mary's and Blessing Hospitals, Quincy, Ill., shortly before his death.

A diplomate of the American Board of Pathology, Dr. Milstead was a member of numerous medical organizations, and was active in their proceedings. He became a Fellow of the American College of Physicians in 1936.

WILLARD D. KLINE, M.D., F.A.C.P.

## COLONEL ROBERT D. HARDEN, M.C., USA

Colonel Robert DuRant Harden, Medical Corps, USA, Retired, F.A.C.P., died August 6, 1947, at Pratt General Hospital, Coral Gables, Fla., where he had been taken from his home in Marathon, Fla.

Born in 1888 in Commerce, Ga., and graduated from Atlanta College of Physicians and Surgeons in 1911, Dr. Harden was commissioned a First Lieutenant, Medical Corps, Regular Army, May, 1915, after fifteen months' service in the Medical Reserve Corps. He served in France, 1918; at Letterman General Hospital, San Francisco, California; as Assistant Corps Area Surgeon of First Corps Area; and three different times in the Office of the Surgeon General, Washington, D. C., receiving a letter of commendation from the Surgeon General for services as Assistant and Chief of the Finance and Supply Division.

In 1928 Dr. Harden was awarded the degree of Master of Public Health by Harvard University. Because of his interest in public health work he was made Assistant Superintendent and Superintendent of Gorgas Hospital, Panama, and received the Legion of Merit award for these three years of service. Colonel Harden was chosen Commanding Officer of Crile General Hospital, Cleveland, Ohio, upon its establishment. Under his guidance this installation increased its bed capacity, maintained high standards of medical care, and developed a most cordial relationship with the City of Cleveland. For unselfish devotion to this duty he was awarded the Oak Leaf Cluster to the Legion of Merit, March, 1946. He retired March 31, 1946.

Colonel Harden was a Fellow of the American College of Surgeons, and of the American Public Health Association. He was elected a Fellow of the American College of Physicians in 1929.

## DR. H. CLIFF SAULS

H. Cliff Sauls, M.D., F.A.C.P., of Atlanta, Ga., died on July 15, 1947. Dr. Sauls was born in Cobb County, Ga., on February 28, 1887. He was graduated in 1913 from the Medical Department of Emory University, which was then known as the Atlanta College of Physicians and Surgeons. He served in World War I as a Captain in the Medical Corps, being a member of the first Emory Unit. He was Associate Professor of Medicine at Emory University and served on the staffs of the Piedmont and Grady Memorial Hospitals in Atlanta, and the Scottish Rite Hospital for Crippled Children in Decatur. He was a member of the Fulton County and Georgia State Societies and of the Southern Medical Association; and a Fellow of the American Medical Association. Dr. Sauls was elected to Fellowship in the American College of Physicians in 1928 and was a diplomate of the American Board of Internal Medicine.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
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